Targeting KRAS-Mediated Pathways: Challenges of Feedback and Resistance

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Abstract

KRAS mutations are among the most common oncogenic drivers in human cancer, affecting switch control pathways that regulate cell growth, survival, and metabolism. Mutations in KRAS interfere with this regulation by keeping the protein in an active state, which causes constant signaling and is linked to cancers like pancreatic, lung, and colorectal cancer. Although significant progress has been made in developing KRAS-target therapies, many approaches focus on static protein structures and may not fully capture its dynamic behavior within living cells. This paper investigates how KRAS mutations affect signaling pathways, with a particular focus on the MAPK pathway and its role in tumor progression and therapeutic resistance. A literature-based methodology was used, focusing on recent peer-reviewed studies with strong mechanistic and experimental evidence, while excluding outdated or non-translational models. The analysis shows that different intervention points in the MAPK signal transduction pathway vary in their ability to shut down oncogenic signaling and prevent pathway reactivation. This question is critical because KRAS mutations drive sustained activation of the MAPK pathway, which is vital for determining whether treatments will fail due to pathway reactivation (e.g., alternative signaling routes or errors in feedback mechanisms). By understanding how targeting different points in the pathways affects both initial suppression and long-term reactivation, this paper allows for innovations and findings of new therapeutic strategies.

Introduction

KRAS (Kristen Rat Sarcoma Viral Oncogene Homolog) is a protein that helps control cell growth and signaling. Under normal conditions, it acts like a switch that turns signaling pathways on and off when a cell receives the right signals. Problems happen when KRAS becomes mutated, because the protein can get stuck in the “on” position, causing cells to keep growing and dividing when they should not. These KRAS mutations are very common in cancers like pancreatic, lung, and colorectal cancer, which is why KRAS has been such an important target in cancer research. Because KRAS plays such a central role in cell signaling, even small changes in its activity can have major effects on cell behavior. This also helps explain why KRAS has been difficult to target with drugs, since the protein is so tightly regulated and essential to normal cellular function.

The primary focus of current research on KRAS is to understand how KRAS interacts with critical biological systems as an oncogene. KRAS regulates essential signaling pathways, including MAPK (Mitogen-Activated Protein Kinase), ERK (Extracellular Signal-Regulated Kinase), and PI3K (Phosphoinositide 3-kinase). These pathways control vital processes such as cell division, metabolism, and survival. Mutations in KRAS cause various complications in cellular signaling, including persistent activation of pathways and tumor growth, which results in reduced responsiveness to therapy. In response, researchers have investigated KRAS-targeted

therapeutic strategies, including mutation-specific inhibitors and combination therapies to disrupt KRAS signaling. Although there has been significant progress, KRAS remains a tough target for treatment because it strongly binds GTP (guanosine triphosphate) and GDP (guanosine diphosphate), and the signaling networks it controls are highly complex.

Even though there has been a lot of progress in targeting KRAS, most current research focuses on designing drugs that bind to one specific, static structure of the protein. In reality, KRAS inside a living cell is constantly changing shape, moving between different locations on the cell membrane, and interacting with other proteins. This means many drugs may be designed for a version of KRAS that does not fully represent how it behaves in cells. A major gap in the field is understanding how these changes affect drug binding and effectiveness, and whether targeting KRAS in a more realistic way could lead to better treatments and strategies.

Methodology

This paper was designed to identify credible, relevant, and current literature related to KRAS-driven signaling and the role of the MAPK pathway in cancer progression and treatment resistance. To ensure that sources selected directly address the research question, specific inclusion and exclusion criteria were established. Primary research papers and review articles from reputable scientific journals, including *Nature Reviews Cancer,* were included. Because this study focuses on the relationship between KRAS mutations and MAPK signaling, selected articles were required to discuss KRAS-driven pathways, the MAPK signaling cascade, or therapeutic strategies targeting components of the MAPK pathway. Studies that examine drugs or interventions targeting specific points of the MAPK pathway were prioritized. Articles that measured pathway activity or evaluated the effectiveness of different interventions were also included.

On the other hand, with the exception of a review article that was used to introduce the concept of the KRAS protein, all of the other selected articles are within ten years. Older articles that fall outside of this range to ensure that the analysis reflected the current understanding of the mechanism by which the KRAS proteins contribute to the oncogenic signaling pathways. In addition, articles not peer-reviewed and other types of publications like conference abstracts were excluded to make sure that the paper extracts information from credible sources with appropriate references. Moreover, studies lacking experimental or mechanistic data on pathways were excluded. Because this paper focuses on understanding how MAPK signaling is suppressed and subsequently reactivated, studies were required to provide mechanistic insight into pathway regulation, feedback signaling, or therapeutic resistance. Finally, articles that used models not representative of human KRAS mutant cancers were excluded to maintain the amount of translational relevance the papers have.

Context and Mutation Types

KRAS is one of the most frequently mutated oncogenes in human cancer cells. KRAS is a member of the RAS family of small GTPases that functions as a membrane-associated signaling "switch." In normal cells, KRAS switches between two states: it is inactive when bound to guanosine diphosphate (GDP) and active when bound to guanosine triphosphate (GTP). The switching process enables control over cell signaling, allowing it to be turned on or off. This switch is controlled by guanine nucleotide exchange factors, which promote guanosine triphosphate loading, and by GTPase-activating proteins, which accelerate guanosine triphosphate hydrolysis and help return KRAS to its inactive state (Choucair et al., 2025; Zhu et al., 2022). This cycling process is important because it allows KRAS signaling to be activated only when the cell receives the appropriate growth signals.

When KRAS is in its active GTP-bound state, it doesn't just turn on one pathway; it activates several downstream signaling routes that control cell growth. survival, metabolism, movement, and invasion. Two major downstream pathways are the RAF-MEK-ERK pathway and the PI3K-AKT-mTOR pathway (Choucair et al., 2025; Zhu et al., 2022). KRAS also signals through the Ral guanine nucleotide dissociation stimulator (Ral-GEF/RalA-RalB) pathway, which is linked to cytoskeletal organization, vesicular trafficking, cell movement, and invasion (Choucair et al., 2025). These pathways manage many important functions in cells; mutations that keep KRAS always active can greatly encourage tumor growth by constantly turning on these signaling pathways, which results in uncontrolled cell growth and survival, especially when KRAS remains active for too long.

KRAS mutations are not evenly distributed across cancer types. They are especially common in pancreatic ductal adenocarcinoma, colorectal cancer, and non-small cell lung cancer. Choucair et al. report KRAS mutation frequencies of 82.1% in pancreatic ductal adenocarcinoma, about 40% in colorectal cancer, and 21.2% in non-small cell lung cancer. Zhu et al. report approximately 90% in U.S. pancreatic ductal adenocarcinoma and approximately 89% in Chinese pancreatic ductal adenocarcinoma; 45% in U.S. colorectal cancer and 49% in Chinese colorectal cancer; and 35% in U.S. lung adenocarcinoma compared with approximately 13% in Chinese lung adenocarcinoma (Choucair et al., 2025; Zhu et al., 2022). These values differ because the studies use different datasets and sometimes describe different cancer categories. For example, lung adenocarcinoma is a subtype of non-small cell lung cancer, so lung adenocarcinoma data should not always be treated as identical to data on non-small cell lung cancer.

Not only do mutation frequencies differ between cancers, but the dominant KRAS mutation types can also vary by tissue. In pancreatic ductal adenocarcinoma, G12D is one of the most common KRAS variants. In colorectal cancer, G12D and G12V are common variants. In lung adenocarcinoma and non-small cell lung cancer, G12C is the dominant KRAS subtype (Choucair et al., 2025; Zhu et al., 2022). These differences matter because KRAS mutation

subtypes can influence downstream signaling behavior and treatment options. For example, Choucair et al. report that G12C and G12V mutations may preferentially activate RalA/RalB signaling, while G12D mutations may show stronger PI3K-AKT-mTOR pathway activation (Choucair et al., 2025). This means that different KRAS mutations may not drive cancer in exactly the same way. These differences are important, as they influence both tumor biology and therapeutic strategies, including the selection of targeted therapies and the development of personalized treatment plans for patients with these specific mutations.

Most oncogenic KRAS mutations occur at specific hotspot codons, particularly codons 12, 13, and 61. These positions are critical to KRAS's ability to hydrolyze GTP and return to its inactive state. Mutations at these codons disrupt the normal regulatory cycle that turns KRAS off. Codon 12 mutations are the most common overall (Choucair et al., 2025). These hotspot locations are important because they affect KRAS's ability to hydrolyze guanosine triphosphate and return to its inactive state. When the KRAS proteins are mutated, they remain in an active GTP-bound state for longer periods of time. In all cases when there are mutations, they cause prolonged signaling pathways and contribute to cancer development (Choucair et al., 2025; Zhu et al., 2022).

Although KRAS mutations are often discussed as a single category, different variants can behave differently at the biochemical and signaling level. For example, some variants may preferentially activate particular downstream pathways. Evidence summarized by Chourcair et al. (2025) suggests that KRAS G12C and G12V mutations may show stronger activation of Ral signaling pathways, while G12D mutations may more strongly activate P13K-AKT-mTOR signaling. These variations in pathway activation can affect how tumors behave and how they respond to treatment.

KRAS mutations play a central role in several major cancers, particularly pancreatic, lung, and colorectal cancers, but these cancers differ in mutation frequency, dominant KRAS variants, and associated genetic alterations. Understanding the difference is important for developing targeted therapies and for explaining why KRAS-driven cancers cannot be treated as a single uniform disease.

Structure and Signaling Mechanisms

Domain Architecture, Isoforms, and Membrane Localization

KRAS exists as two major splice isoforms, KRAS4A and KRAS4B. Both share a nearly identical catalytic GTPase G-domain, which contains the structural elements responsible for nucleotide binding and hydrolysis. However, the isoforms differ significantly in their C-terminal hypervariable region (HVR) (Garg et al., 2026). The HVR determines how KRAS interacts with cellular membranes and therefore strongly influences its signaling behavior. Structural studies emphasize that while the G-domain performs the enzymatic switching function, the HVR acts as

the membrane-targeting module that anchors KRAS to the plasma membrane, where signaling happens (Garg et al., 2026). Membrane localization depends on several post-translational modifications at the C-terminus, which are referred to as CAAX processing. This process includes: Prenylation of the cysteine residue, Proteolytic removal of the terminal amino acids, and Carboxymethylation. Together, these modifications create a hydrophobic tail that allows KRAS to associate with cellular membranes (Garg et al., 2026). The two isoforms use slightly different strategies for membrane binding. KRAS4B contains a strong polybasic region in its HVR that electrostatically interacts with negatively charged phospholipids in the membrane. On the other hand, KRAS4A can undergo palmitoylation, adding another lipid group that enhances membrane association (Garg et al., 2026). Additional proteins also influence KRAS membrane trafficking such as the chaperone PDEδ because its additional lipid modification can't easily fit into the PDEδ binding pocket.

Atomic Switch Elements and Regulatory Proteins

At the molecular level, KRAS activity is controlled by structural elements within the G-domain. The P-loop binds the phosphate groups of the nucleotide, while the flexible switch 1 and 2 regions change conformation depending on whether GDP or GTP is bound (Miura, 2025). These structural changes regulate interactions with two major classes of regulatory proteins: GEFs (Guanine nucleotide exchange factors) promote GDP release and GTP loading, turning KRAS on, and GAPs (GTPase-activating proteins) accelerate GTP hydrolysis, turning KRAS off. Two well-known examples are SOS1, a major GEF that activates KRAS downstream of receptor tyrosine kinases (RTKs), and NF1, a GAP that promotes KRAS inactivation (Miura, 2025). RTK signaling feeds into the KRAS activation cycle through adaptor networks. For instance, SHP2 acts as a key signaling node that links activated receptors to RAS activation and the broader RAS-RAF-MEK-ERK pathway (Choucair et al., 2025).

How Hotspot Mutations Alter the Nucleotide Cycle

Most cancer-associated KRAS mutations occur at codons 12, 13, or 61, which together account for the vast majority of KRAS alterations (Miura, 2025). These mutations affect the nucleotide cycle in different ways. Some mutations, such as those at G12 or Q61, interfere with GTP hydrolysis, which leads to KRAS remaining active for longer periods. Others alter how quickly nucleotides exchange. A specifically important example is KRAS(G12C). While oncogenic KRAS is usually described as permanently active, studies of G12C inhibitors showed that this mutant still undergoes nucleotide cycling. Covalent inhibitors bind to a cysteine residue created by the mutation within the switch-2 pocket and stabilize the inactive GDP-bound state. As KRAS cycles between states, the inhibitor slowly traps the protein in the inactive conformation (Miura, 2025). Not all mutations behave the same way. For example, codon 146 mutations, which are frequently observed in colorectal cancer, primarily increase GEF-mediated nucleotide exchange rather than impairing hydrolysis. This difference suggests that therapies targeting upstream exchange mechanisms may especially be relevant for these variants (Choucair et al., 2025).

KRAS Nanoclusters and Spatial Organization

KRAS signaling is influenced not only by its biochemical activity but also by how it is organized on the plasma membrane. Instead of being evenly spread across the membrane, KRAS molecules tend to group together into small, temporary clusters known as nanoclusters. These clusters function as concentrated signaling platforms where KRAS can more efficiently interact with downstream proteins (Garg et al., 2026). KRAS nanoclusters form and break apart very quickly, often within fractions of a second. Even though they are short-lived, they play an important role in amplifying signaling because they bring multiple signaling molecules into close proximity. Within these clusters, KRAS can effectively recruit and activate downstream effectors such as RAF, helping initiate MAPK pathway signaling. This spatial organization also helps explain why blocking downstream components of the pathway does not always completely shut down signaling. Because KRAS activity originates at the membrane, strong upstream signals can quickly generate new nanoclusters and restart signaling. As a result, drugs that target downstream proteins like MEK or ERK may temporarily suppress the pathway but not fully prevent it from becoming active again (Choucair et al., 2025).

MAPK Cascade Activation and Feedback Regulation

When KRAS is in its GTP-bound active state at the membrane, it initiates the MAPK signaling cascade by recruiting and activating RAF kinases. Activation of RAF typically involves RAF dimerization, which is promoted by binding to active RAS. Once RAF is activated, the signaling cascade proceeds through a series of phosphorylation events: RAF phosphorylates MEK, MEK phosphorylates ERK, ERK phosphorylates many downstream targets. Activated ERK then regulates a wide range of cellular processes by phosphorylating transcription factors and other signaling proteins. Through these actions, the pathway controls important functions such as cell growth, survival, and proliferation (Miura, 2025). However, the MAPK pathway also contains built-in negative feedback mechanisms. When ERK becomes active, it can suppress upstream signaling components, including receptors and adaptor proteins that normally activate the pathway. These feedback loops help prevent excessive signaling under normal conditions. Interestingly, when drugs inhibit MEK or ERK, these feedback controls are removed. Without this suppression, receptor tyrosine kinases can become more active and drive the pathway again. This phenomenon, which is known as feedback relief, usually leads to rebound signaling. For example, studies in colorectal cancer have shown that EGFR signaling can reactivate the MAPK pathway even when KRAS(G12C) inhibitors are used (Choucair et al., 2025). This shows how upstream receptor signaling can limit the effectiveness of targeted therapies and contribute to drug resistance.

Structural Insights and Intervention Points

Understanding how KRAS is structured and regulated helps explain why different therapeutic strategies can produce very different outcomes. One approach involves directly targeting KRAS itself. In theory, this strategy blocks signaling at its source by preventing KRAS from activating the entire RAF-MEK-ERK cascade. However, direct inhibition is challenging

because many KRAS mutants lack clear drug binding pockets, and different mutations behave differently (Miura, 2025). Another strategy focuses on the upstream machinery that activates KRAS, including proteins such as SHP2 and SOS1, which help promote nucleotide exchange. By reducing the rate at which KRAS switches from GDP to GTP, this approach can enhance the effects of direct KRAS inhibitors. For instance, recent studies suggest that SOS1 inhibitors can reduce the rebound activation of ERK that sometimes occurs after treatment with KRAS(G12C) inhibitors (Miura, 2025). Combining these approaches could help prevent the pathway from reactivating. KRAS signaling can also be influenced by proteins that regulate KRAS stability. One study found that the protein NDRG3 interacts with KRAS and helps stabilize it through a deubiquitination process involving the enzyme USP9X. When NDRG3 was depleted, ERK signaling decreased in KRAS mutant cells, suggesting that targeting KRAS stabilization mechanisms could represent another possible therapeutic strategy (Garg et al., 2026). Overall, these findings highlight that KRAS-driven signaling is controlled by multiple interconnected factors, including protein structure, nucleotide cycling, membrane organization, and pathway feedback mechanisms. Because of this complexity, successful therapeutic strategies often need to consider several intervention points rather than targeting just a single part of the pathway.

Current Strategies

The MAPK signaling pathway plays a crucial role in the regulation of cell proliferation and survival. In many cancers, mutations in the KRAS protein lead to the constant activation of the pathway, leading to uncontrolled cell growth. Because KRAS is an early step in the signaling pathway, a KRAS mutation can keep activating the rest of the pathway even when the signals that usually start the pathway aren't present (Huang et al., 2021). To try and circumvent this, most therapies focus on inhibiting different nodes in the MAPK pathway. The efficacy of these intervention therapies vary depending on how completely they shut down the ERK activity and how easily the pathway can reactivate (Huang et al., 2021).

One of the strategies for targeting the MAPK signaling is inhibiting MEK. These inhibitors are one of the earliest strategies to target the MAPK signaling pathway because MEK occupies a specific position in the pathway, which results in fewer off-target effects compared to its other upstream signaling components. In theory, the inhibition of MEK should prevent ERK activation, which should then block transcriptional programs limiting tumor growth. In practice, the inhibition of MEK only shuts down MAPK signaling at first, and then it later reactivates it. Normally, ERK helps regulate the pathway through negative feedback. When MEK is inhibited, the upstream receptors become overactive and stimulate other RAS proteins, restoring signaling. Because of the negative feedback loop, the pathway often reactivates quickly even with the drug being present (Misale et al., 2015).

Another approach that has been explored is targeting RAF kinases. RAF proteins act as a link between RAS activation and the rest of the MAPK cascade. In theory, inhibition of the RAF protein should prevent the signal from KRAS from reaching MEK and ERK. RAF inhibitors have been effective in cancers that are driven by BRAF mutations; however, they are not as effective in cancers driven by KRAS mutations. One reason for this is that KRAS can activate multiple RAF isomers (ARAF, BRAF, and CRAF) that function as dimers. Since RAF inhibitors can only block one of these signaling through MEK, ERK can continue, limiting the effectiveness of RAF inhibition in KRAS mutant cancers (Huang et al., 2021).

More recently, drug development has shifted towards directly targeting the mutant KRAS itself. This is often the primary oncogenic driver in these types of cancers. KRAS has been considered undruggable because of its high affinity for GTP/GDP, but the discovery of covalent inhibitors targeting the KRAS G12C mutation has led to the development of drugs such as Sotorasib and Adagrasib (Huang et al., 2021). These inhibitors bind to the mutant cysteine residue and trap KRAS in an inactive GDP-bound state (Canon et al., 2019). The direct inhibition of KRAS can produce a stronger suppression of the MAPK signaling pathway than downstream inhibitors since it prevents the initial activation step that causes the cascade of signaling. One fault of KRAS inhibitors is that tumors can often adapt feedback mechanisms that reactivate the pathway.

Another strategy involves targeting signaling components that are upstream of KRAS, such as SHP2 and SOS1. These proteins regulate the activation of RAS downstream of RTKs. Inhibiting SHP2 and SOS1 can reduce the ability of cells to reactivate RAS signaling after the inhibition of the pathway (Misale et al., 2015). This strategy is often used in combination with MEK inhibitors. The inhibition of SHP2 and SOS1 reduces the negative feedback loop that makes the inhibition of MEK virtually useless. Many researchers believe that single agent inhibition is not sufficient to successfully suppress the signaling pathway. This approach is sometimes referred to as vertical inhibition and involves blocking both the oncogenic driver and downstream signaling components to prevent reactivation (Misale et al., 2015).

Overall, the effectiveness of therapies targeting the MAPK pathway in KRAS mutant cancers depend on where the pathway is inhibited. Inhibition that occurs downstream, such as MEK inhibitors, often leads to rapid pathway reactivation due to feedback mechanisms. Direct KRAS inhibitors are able to more effectively target the primary oncogenic driver, although they still face difficulties with alternative routes. Because of these difficulties, the current approaches are based on combination therapies that target more points on the pathway to make the suppression more long-lasting (Canon et al., 2019).

Therapeutic Challenges and Future Directions

Targeted therapies against KRAS have advanced significantly over the last few decades, and yet current treatments are still facing major therapeutic limitations. While the two FDA-approved inhibitors, Sotorasib and Adagrasib, are making progress in clinical trials by showing meaningful response rates and improvements, they eventually result in resistance, which is a common issue in KRAS-targeting inhibitors. Resistance to KRAS inhibition occurs through several mechanisms, including primary, acquired, and adaptive resistance, and is a primary concern that scientists deal with in targeting KRAS. Overcoming drug resistance will be crucial for improving patient outcomes, especially given the diversity of mutation mechanisms that still need to be investigated.

Primary resistance has been hypothesized to correlate with co-mutation and KRAS mutation, and is responsible for the initial unresponsiveness to inhibitor treatments. According to Isermann et al., this occurs in around 9-24% of all patients treated with KRAS inhibitors. For instance, a clinicogenomic study has shown that patients treated with Sotorasib or Adagrasib showed co-mutations in KEAP1, SMARCA4, and CDKN2A, which are several important tumor suppressors or regulators of cell survival and proliferation. Although several studies have suggested that those tumors do not have additional resistance mutations prior to treatment, it is unclear how primary resistance works.

Acquired resistance plays a role when mutations emerge under the pressure of KRAS inhibition, typically occurring 4-6 months after treatment. Mutations in several codons can affect the ability of drugs to bind and reduce the effectiveness of inhibitors designed for KRAS. Additional alterations in RTK pathways and gene amplifications further promote resistance and tumor progression. There are several mutation pathways that showcase how heterogeneous KRAS can impose and are an area of interest for scientists studying resistance. In contrast, adaptive resistance refers to the ability of tumor cells to circumvent KRAS-targeted therapy through feedback mechanisms rather than genetic mutations like acquired resistance. A common type is the reactivation of the RAS-MAPK signaling pathway, which allows cancer cells to proliferate with KRAS G12C inhibition. Even when mutated KRAS activity is blocked, other mechanisms get activated and result in overexpression of receptor tyrosine kinase (RTKs), leading to similar activity of cell proliferation that KRAS activity would have caused.

With the high prevalence of resistance to KRAS inhibitors, the field of combination therapies is rapidly expanding (Choucair et al., 2025). An extensively studied therapy involves EGFR antibodies that have shown robust antitumor effects, particularly in colorectal cancer (CRC). For instance, in the Phase 1b KRYSTAL-1 study, combining Adagrasib with Cetuximab reported a 27.8% increase in objective response rate (ORR), a measure in cancer treatment of the percentage of patients whose tumors shrink or disappear after therapy, when treated with the combination therapy. Another potent combination type is immunotherapy-based combinations. Some KRASG12C inhibitors have been combined with an anti-PD-1/PD-L1 therapy to promote

durable T-cell-mediated antitumor responses. An example of this type of therapy involves combining Sotarasib and anti-PD-L1 drug, which resulted in complete tumor regression that persisted for over 2 months after the end of treatment. There were 24 ongoing clinical trials with this type of combination strategy as of early 2025 (Isermann et al., 2025). Chemotherapy, as a standard of care, also has combination strategies. While preclinical studies have shown support for an observable reduction in tumor growth, it's unclear whether it's truly due to the synergy between KRAS inhibitors and chemotherapeutics or simply that chemotherapy is targeting rapidly replicating cells that happen to be resistant to KRAS inhibitors, presenting a result that can not be differentiated from synergy.

While combination therapy is more promising compared to monotherapy because of its effects in regulating various mechanisms, it needs to be carefully monitored for its dosing capacity. Toxicities can arise from being off-target, in which several drugs have amplified side effects and pose greater threats as combination therapy aims to target more mechanisms (Zhu et al., 2022). Recent strategies have continued to focus on expanding the efficacy of KRAS therapies and addressing resistance to FDA-approved inhibitors. From synthesizing new KRAS inhibitors to target additional mutations to coming up with combination therapies that will possibly inhibit regulatory mechanisms simultaneously, the path that researchers are taking continues to diversify as more KRAS mechanisms are discovered. Many of the strategies utilized, including immunotherapy or even nucleic acid-based therapies, are in preclinical or early clinical stages. They are leading the pathway to offer promises for improving patient outcomes.

Conclusion

Overall, the evidence suggests that the effectiveness of therapies targeting KRAS-driven cancer depends largely on where intervention occurs within the MAPK pathway. While downstream inhibitors such as RAF and MEK inhibitors can initially suppress signaling, their effects are often limited by feedback mechanism and pathway reactivation. Direct KRAS inhibitors generally provide an effective suppression because they target the primary oncogenic driver, but they also face challenges from different types of resistance. These findings show that KRAS-driven signaling functions as a complex network rather than a linear pathway, allowing tumors to bypass inhibition through alternative signaling routes. As a result, current research supports combination therapies that target multiple points in the pathway simultaneously. Although these approaches have shown promising results, further research is needed to better understand resistance mechanisms and to optimize treatment combinations. Advances in this area can be critical to durable therapeutic responses and improved outcomes for patients with KRAS-mutant cancers.

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