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KRAS Mutations in Cancer: Molecular Insights, Therapeutic Advances, and Strategies to Overcome Resistance

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ABSTRACT

KRAS mutations are among the most frequent oncogenic alterations in human cancers, with a particularly high prevalence in pancreatic, colorectal, and lung malignancies. These genetic changes disrupt the normal regulation of cell signaling pathways, leading to sustained proliferation, altered metabolism, and resistance to apoptosis. For decades, KRAS was considered beyond the reach of pharmacological intervention, largely due to its structural complexity and strong nucleotide-binding affinity. Recent scientific progress has challenged this notion, resulting in the approval of selective inhibitors that have changed the management of cancers carrying KRAS mutations. Nevertheless, resistance to these agents continues to emerge through tumor heterogeneity, compensatory signaling, and secondary genetic events. Current research is focused on developing next-generation inhibitors, RNA-based therapies, degraders, and immune-based approaches to address these challenges. In addition, artificial intelligence and advanced drug delivery technologies are expanding the possibilities for therapeutic innovation. Pharmacists and clinicians play a critical role in integrating biomarker testing, therapeutic monitoring, and patient support to optimize treatment outcomes and improve access to targeted therapies. This review examines the molecular basis of KRAS-driven cancers, evaluates the progress of pharmacological strategies, and highlights the ongoing challenges and opportunities for future research and clinical practice.

Keywords: *KRAS mutations, oncogenes, targeted therapy, resistance, precision oncology, drug development*.

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1. INTRODUCTION

Cancer remains one of the leading causes of morbidity and mortality worldwide, accounting for nearly ten million deaths in 2020 according to the World Health Organization [1]. The disease arises from the accumulation of genetic and epigenetic changes that disrupt normal cellular homeostasis, promoting uncontrolled proliferation, evasion of apoptosis, and metastatic spread [2]. Among the many genes implicated in carcinogenesis, the RAS family has emerged as one of the most critical. This family includes HRAS, NRAS, and KRAS, which encode small GTP-binding proteins that regulate

fundamental signaling pathways responsible for cell growth and survival [3].

1.1. Significance of KRAS Mutations

Of these, KRAS has attracted the greatest clinical attention due to its high mutation frequency and its pivotal role in several of the most lethal cancers. KRAS mutations are detected in more than 90% of pancreatic ductal adenocarcinomas, approximately 45% of colorectal cancers, and around 30% of non-small cell lung cancers [4–6]. These alterations typically occur at codons 12, 13, and 61, which lock the protein in an active GTP-bound conformation. This results in continuous activation of downstream pathways such as RAF–MEK–ERK and PI3K–AKT–mTOR, driving oncogenesis through sustained mitogenic and anti-apoptotic signals [7].

1.2. Historical Challenges in Targeting KRAS

Despite being recognized as a key driver of cancer for over four decades, KRAS long resisted pharmacological targeting. Its structure presents challenges for drug design, as the protein binds GTP and GDP with picomolar affinity and lacks deep binding pockets suitable for small-molecule inhibitors [8]. Because of this, KRAS was historically labeled as "undruggable," and research shifted toward targeting downstream effectors such as RAF or MEK [9]. However, these strategies achieved limited clinical benefit due to feedback activation and compensatory signaling networks.

1.3. Recent Advances

The therapeutic landscape began to change with the development of covalent inhibitors capable of selectively binding to KRAS G12C, a mutation prevalent in subsets of lung and colorectal cancers [10]. Agents such as sotorasib and adagrasib have demonstrated meaningful clinical activity and gained regulatory approval, marking the beginning of a new era in precision oncology [11]. These successes have stimulated intense research into inhibitors for other KRAS variants, including G12D and G12V, which remain significant unmet clinical needs [12].

1.4. Novel Therapeutic Approaches

Beyond direct inhibition, novel therapeutic strategies are being explored to target KRAS-driven tumors. These include degraders that promote proteasomal destruction of the protein, antisense oligonucleotides and RNA interference approaches that suppress KRAS expression, and immunotherapy-based strategies that exploit KRAS-derived neoantigens [13,14]. Artificial intelligence–driven drug discovery and advanced delivery technologies, such as nanoparticle systems, are also expected to accelerate the development of next-generation KRAS-targeted therapies [15].

1.5. Clinical and Pharmacy Implications

The clinical relevance of KRAS extends beyond biology and therapeutics. Biomarker testing for KRAS mutations is now an essential part of diagnostic and treatment decision-making, particularly in colorectal and lung cancer [16]. Pharmacists and clinicians play a central role in integrating these molecular findings into patient care, ensuring appropriate therapy selection, monitoring adverse effects, and addressing the significant financial burden associated with targeted therapies [17].

This review provides a comprehensive analysis of KRAS in cancer, beginning with its molecular biology and role in major tumor types. It then explores current and emerging pharmacological interventions, the mechanisms of therapeutic resistance, and the clinical implications of KRAS targeting in oncology practice. By consolidating recent advances, challenges, and future perspectives, the review aims to contribute to ongoing efforts to optimize KRAS-directed cancer therapy and to improve patient outcomes.

2. MOLECULAR BIOLOGY OF KRAS

The KRAS gene is located on chromosome 12p12.1 and encodes a 21 kDa guanosine triphosphate (GTP)-binding protein that functions as a molecular switch in critical signaling pathways [23]. Like other members of the RAS family, KRAS cycles between an active GTP-bound state and an inactive guanosine diphosphate (GDP)-bound state [24]. This tightly regulated cycle is controlled by guanine nucleotide exchange factors (GEFs), which facilitate the replacement of GDP with GTP, and GTPase-activating proteins (GAPs), which promote GTP hydrolysis [25]. Through this mechanism, KRAS precisely regulates downstream signaling cascades that control cellular proliferation, differentiation, survival, and metabolism [26].

2.1. Impact of KRAS Mutations

Mutations in KRAS disrupt this regulatory balance. The most frequent alterations occur at codons 12, 13, and 61 (G12C, G12D, G12V, G13D, Q61H), which impair intrinsic GTPase activity and prevent GAP-mediated inactivation [27]. As a result, KRAS remains locked in the active GTP-bound state, continuously transmitting proliferative and survival signals to downstream effectors [28]. This constitutive activation explains the oncogenic potential of KRAS and its central role in the pathogenesis of multiple cancers [29].

3. DOWNSTREAM SIGNALING PATHWAYS

Activated KRAS engages several major signaling networks that drive oncogenesis.

3.1. MAPK/ERK Pathway

Active KRAS recruits RAF kinases to the cell membrane, initiating the RAF–MEK–ERK cascade. This pathway promotes cell cycle progression and proliferation [30]. Mutational activation of KRAS thus results in unchecked mitogenic signaling, which is particularly relevant in colorectal and lung cancers [31].

3.2. PI3K/AKT/mTOR Pathway

KRAS also activates phosphoinositide-3-kinase (PI3K), leading to AKT and mTOR activation. This pathway promotes cell survival, inhibits apoptosis, and regulates metabolic reprogramming [32]. Hyperactivation of PI3K–AKT contributes to therapeutic resistance in KRAS-mutant cancers [33].

3.3. Ral–GEF Pathway

Through interaction with Ral guanine nucleotide dissociation stimulators, KRAS influences cytoskeletal organization, vesicle trafficking, and metastatic potential [34]. This pathway is increasingly recognized in pancreatic ductal adenocarcinoma progression [35].

The simultaneous activation of these pathways results in a tumor phenotype characterized by rapid growth, invasion, and resistance to standard therapies.

4. CLINICAL RELEVANCE OF KRAS MUTATIONS

The frequency and type of KRAS mutations vary across malignancies. In pancreatic ductal adenocarcinoma, more than 90% of cases harbor KRAS mutations, most often G12D or G12V [36]. In colorectal cancer, KRAS mutations occur in approximately 40–45% of patients, with G12D and G13D being most common [37]. Non-small cell lung cancer shows KRAS mutations in 25–30% of cases, dominated by the G12C variant [38]. Mutations are also observed in biliary tract cancers, endometrial cancers, and certain hematologic malignancies, though at lower frequencies [39].

4.1. Therapeutic Implications

These mutations not only drive oncogenesis but also carry clinical significance. For example, KRAS mutations in colorectal cancer predict resistance to anti-EGFR therapies such as cetuximab and panitumumab [40]. Similarly, the identification of KRAS G12C mutations in lung cancer has enabled the use of targeted inhibitors such as sotorasib and adagrasib [41]. Thus, understanding the molecular biology of KRAS directly informs therapeutic decision-making and precision oncology strategies.

5. FREQUENCY OF KRAS MUTATIONS IN MAJOR CANCERS

Cancer Type	Prevalence of KRAS Mutations	Most Common Variants	Clinical Significance
Pancreatic ductal adenocarcinoma	>90%	G12D, G12V	Early oncogenic driver; no approved targeted therapy
Colorectal cancer	40–45%	G12D, G12V, G13D	Predicts resistance to anti-EGFR therapy
Non-small cell lung cancer	25–30%	G12C	Targetable with sotorasib and adagrasib
Biliary tract cancer	15–20%	G12D, G12V	Poor prognosis; potential trial enrollment
Endometrial cancer	10–15%	G12D, Q61H	Associated with PI3K/PTEN pathway alterations
Gastric, ovarian, hematologic	<10%	Variable	Under investigation for targeted strategies

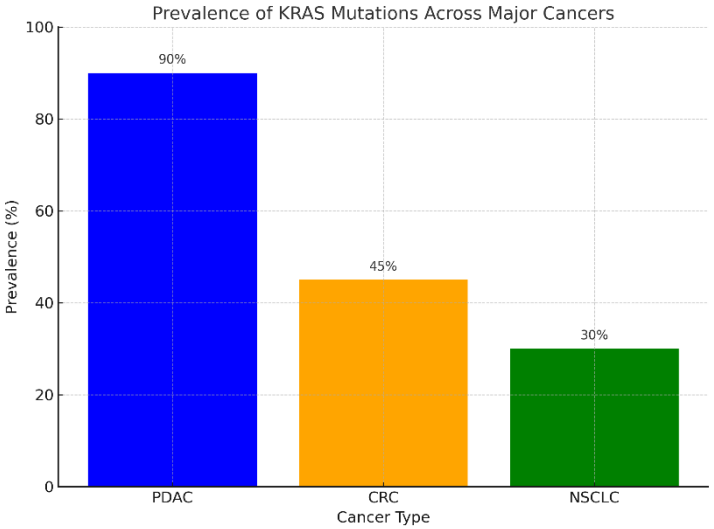

Figure 1: A comparative schematic showing the prevalence of KRAS mutations across major cancers. Each cancer type is represented by a pie chart illustrating mutation frequency and variant distribution, highlighting the dominance of G12D in pancreatic cancer, G12D/G13D in colorectal cancer, and G12C in lung cancer.

6. KRAS MUTATIONS IN MAJOR CANCERS

KRAS mutations are among the most clinically significant oncogenic alterations in solid tumors. They occur across a wide spectrum of cancers but show particularly high prevalence in pancreatic ductal adenocarcinoma, colorectal cancer, and non-small cell lung cancer. Each tumor type displays unique mutation patterns and clinical implications, highlighting the importance of tumor-specific context in therapeutic decision-making.

6.1. Pancreatic Ductal Adenocarcinoma (PDAC)

Pancreatic ductal adenocarcinoma is one of the deadliest malignancies, with a five-year survival rate below 10% [42]. More than 90% of cases harbor KRAS mutations, making it the most frequently mutated gene in PDAC [43]. The majority involve codon 12, with G12D and G12V as the dominant variants [44]. These mutations occur early during tumorigenesis and are thought to represent initiating events in pancreatic carcinogenesis [45].

6.1.1. Molecular and Clinical Features

Constitutively active KRAS in PDAC drives continuous activation of downstream MAPK and PI3K signaling, leading to uncontrolled proliferation and metabolic reprogramming [46]. Furthermore, KRAS mutations in pancreatic cancer are associated with desmoplastic stroma formation and an immunosuppressive tumor microenvironment, which contribute to therapeutic resistance [47]. Unlike KRAS G12C, which has specific inhibitors, the predominant G12D mutation in PDAC remains difficult to target, and treatment continues to rely largely on chemotherapy regimens such as FOLFIRINOX or gemcitabine combinations [48]. Ongoing clinical trials are evaluating G12D-specific inhibitors and mRNA vaccines, but these remain investigational [49].

6.2. Colorectal Cancer (CRC)

Colorectal cancer is the third most commonly diagnosed cancer worldwide. Approximately 40–45% of metastatic CRC cases harbor KRAS mutations, predominantly at codons 12 and 13 [50]. The most frequent variants are G12D, G12V, and G13D [51]. These mutations are mutually exclusive with alterations in NRAS or BRAF, reinforcing their role as primary drivers of tumorigenesis [52].

6.2.1. Clinical Significance

The clinical significance of KRAS mutations in CRC is well established. Patients with KRAS-mutant tumors do not benefit from anti-EGFR monoclonal antibodies such as cetuximab or panitumumab [53]. Consequently, KRAS mutation testing is mandatory before initiating EGFR-targeted therapy [54]. This represents one of the earliest examples of precision oncology in clinical practice. Beyond treatment selection, KRAS mutations are also associated with poor prognosis, shorter progression-free survival, and limited response to standard chemotherapy [55]. Emerging therapies for KRAS-mutant CRC include direct KRAS inhibitors, combination regimens targeting MEK or PI3K pathways, and immunotherapy strategies that exploit KRAS-derived neoantigens [56]. However, resistance remains a major challenge, particularly due to feedback

activation of alternate signaling cascades [57].

6.3. Non-Small Cell Lung Cancer (NSCLC)

Non-small cell lung cancer accounts for approximately 85% of lung cancer cases and is a leading cause of cancer-related deaths globally [58]. KRAS mutations occur in 25–30% of NSCLC, particularly in adenocarcinoma histology [59]. The most common variant is G12C, present in about 13% of NSCLC patients [60]. Other mutations include G12D and G12V, although at lower frequencies [61].

6.3.1. Therapeutic Advances

For decades, KRAS-mutant NSCLC was considered a therapeutic dead end. However, the development of KRAS G12C inhibitors has significantly changed the treatment paradigm. Sotorasib and adagrasib have both demonstrated meaningful clinical responses, leading to their approval for patients with previously treated KRAS G12C-mutant NSCLC [62,63]. Nevertheless, resistance to these agents emerges rapidly, limiting the durability of responses [64].

6.3.2. Co-occurring Mutations

KRAS mutations in NSCLC also co-occur with alterations in TP53, STK11, or KEAP1, which influence treatment outcomes and immune checkpoint inhibitor responsiveness [65]. For instance, KRAS/TP53 co-mutant tumors tend to be more immunogenic, whereas KRAS/STK11 co-mutant tumors often show resistance to immunotherapy [66]. These molecular subsets are now being recognized as distinct clinical entities, guiding personalized treatment strategies.

6.4. Other Cancers

Although less frequent, KRAS mutations are also found in several other malignancies. In biliary tract cancers, mutation rates range from 15% to 20%, with G12D and G12V being most common [67]. Endometrial cancers display KRAS mutations in 10–15% of cases, often in association with PTEN loss or PI3K pathway activation [68]. KRAS alterations have also been reported in gastric cancers, ovarian mucinous tumors, and certain hematologic malignancies, though at lower frequencies [69]. While targeted therapies are not yet established in these settings, the identification of KRAS mutations may inform enrollment into clinical trials.

7. PHARMACOLOGICAL ADVANCES IN TARGETING KRAS

For many years, KRAS was considered beyond the reach of drug development. Its high affinity for guanosine triphosphate and guanosine diphosphate, combined with a relatively smooth protein surface lacking deep binding pockets, led to its classification as “undruggable” [70]. However, advances in structural biology, fragment-based drug design, and covalent chemistry have fundamentally changed this perspective. Today, selective inhibitors, RNA-based therapies, and novel degraders are beginning to alter the therapeutic landscape for patients with KRAS-mutant cancers.

8.1. Historical Approaches

Early therapeutic strategies focused on targeting post-translational modification and downstream signaling rather than KRAS itself.

8.1.1. Farnesyltransferase Inhibitors (FTIs)

KRAS requires prenylation for membrane localization and function. FTIs were developed to block this modification, but clinical trials failed due to compensatory geranylgeranylation that allowed KRAS to bypass farnesylation [71]. While some efficacy was noted in HRAS-driven cancers, FTIs were ineffective against KRAS mutations.

8.1.2. RAF and MEK Inhibitors

Since KRAS directly activates RAF–MEK–ERK signaling, inhibitors of these kinases were investigated as indirect approaches. MEK inhibitors such as trametinib showed modest activity but were limited by rapid feedback activation and toxicity [72]. Combination strategies, including MEK plus PI3K inhibition, improved preclinical results but were poorly tolerated clinically [73].

8.2. Breakthrough: Direct KRAS G12C Inhibitors

A major advance occurred with the identification of a previously hidden pocket adjacent to cysteine 12 in the KRAS G12C mutant. This discovery enabled the design of covalent inhibitors that selectively and irreversibly bind to the mutant cysteine, trapping KRAS in its inactive GDP-bound form [74].

8.2.1. Sotorasib (AMG 510)

The first KRAS G12C inhibitor approved by the U.S. FDA in 2021 for previously treated non-small cell lung cancer [75]. In the CodeBreaK 100 trial, sotorasib demonstrated an objective response rate of 37% and median progression-free survival of 6.8 months [76]. Common adverse events include diarrhea, nausea, and hepatotoxicity.

8.2.2. Adagrasib (MRTX849)

Approved in 2022 for KRAS G12C-mutant NSCLC, adagrasib has shown durable responses with intracranial activity in brain metastases [77]. In the KRYSTAL-1 study, adagrasib produced a response rate of 43% with median progression-free survival of 6.5 months [78].

Both agents represent a paradigm shift, demonstrating that direct inhibition of KRAS is possible. However, clinical benefits are often limited by the emergence of resistance, highlighting the need for next-generation strategies [79].

8.3. Emerging Inhibitors for Non-G12C Variants

While G12C inhibitors mark an important milestone, they target a minority of KRAS-mutant cancers. The most common alterations, particularly G12D and G12V, remain without approved targeted therapies.

8.3.1. KRAS G12D Inhibitors

Recent advances have produced small molecules that selectively target the G12D variant, such as MRTX1133. Preclinical studies demonstrate strong antitumor activity in pancreatic and colorectal cancer models [80]. Early-phase clinical trials are ongoing.

8.3.2. KRAS G12V and Q61H Inhibitors

Though more challenging, compounds designed for these variants are in preclinical development [81]. Structural studies suggest unique binding opportunities that may be exploited for drug design.

8.3.3. Pan-KRAS Inhibitors

Agents that target multiple KRAS mutants, including both G12C and non-G12C variants, are being developed to broaden therapeutic coverage [82].

8.4. Indirect Targeting Strategies

Beyond direct inhibitors, several alternative approaches aim to suppress KRAS function or exploit KRAS-driven vulnerabilities.

8.4.1. SHP2 Inhibitors

SHP2 is a phosphatase required for upstream signaling to KRAS. Inhibitors such as RMC-4630 block KRAS activation and show synergy when combined with KRAS G12C inhibitors [83].

8.4.2. SOS1 Inhibitors

SOS1 is a guanine nucleotide exchange factor that promotes activation of KRAS. Inhibitors of SOS1, such as BI-1701963, are being tested in clinical trials, particularly in combination with MEK inhibitors [84].

8.4.3. Synthetic Lethality Approaches

KRAS-mutant cancers often depend on parallel survival pathways. Inhibiting these pathways, such as DNA damage repair with PARP inhibitors, may enhance antitumor efficacy [85].

8.5. RNA-Based Therapeutics

Targeting KRAS at the transcript level has also shown promise.

8.5.1. Antisense Oligonucleotides (ASOs)

Early ASOs targeting KRAS mRNA showed limited clinical activity, but newer designs with improved stability are in development [86].

8.5.2. siRNA and RNAi Approaches

RNA interference strategies have demonstrated preclinical activity against KRAS-mutant cancers. Lipid nanoparticle delivery systems are being explored to improve clinical translation [87].

8.5.3. mRNA Vaccines

Vaccines targeting KRAS neoantigens, such as G12D or G12V peptides, aim to stimulate immune recognition of tumor cells. Early clinical trials in pancreatic cancer suggest immunogenicity and potential synergy with immune checkpoint inhibitors [88].

8.6. Targeted Protein Degradation

Another innovative approach involves using proteolysis-targeting chimeras (PROTACs) or molecular glues to promote

selective degradation of KRAS. By recruiting the ubiquitin–proteasome system, these molecules could eliminate mutant KRAS protein rather than simply inhibiting its activity [89]. Although still in preclinical stages, this strategy holds considerable promise.

8.7. Combination Strategies

Given the complexity of KRAS signaling, monotherapy is unlikely to achieve durable benefit. Rational combinations are therefore being actively explored, including KRAS inhibitors plus MEK or SHP2 inhibitors [90], KRAS inhibitors plus immune checkpoint blockade (anti-PD-1/PD-L1) [91], and KRAS inhibition with chemotherapy or radiotherapy to enhance sensitivity [92]. These strategies aim to overcome adaptive resistance and improve long-term outcomes.

8. CURRENT AND EMERGING PHARMACOLOGICAL STRATEGIES FOR KRAS-MUTANT CANCERS

Strategy	Agents/Examples	Clinical Status	Key Notes
Farnesyltransferase inhibitors	Tipifarnib, lonafarnib	Failed in KRAS cancers	Bypassed by geranylgeranylation
RAF/MEK inhibitors	Trametinib, selumetinib	Limited efficacy	Resistance and toxicity issues
KRAS G12C inhibitors	Sotorasib, adagrasib	Approved for NSCLC, CRC trials	Durable but resistance emerges
KRAS G12D inhibitors	MRTX1133	Preclinical/early trials	Promising for PDAC, CRC
SHP2 inhibitors	RMC-4630, TNO155	Phase I/II trials	Synergistic with KRAS inhibitors
SOS1 inhibitors	BI-1701963	Phase I trials	Target upstream activation
RNA-based approaches	ASOs, siRNA, mRNA vaccines	Preclinical/early trials	Novel but delivery challenges
Targeted protein degradation	PROTACs, molecular glues	Preclinical	Potential to eliminate KRAS protein
Combination therapies	KRAS + MEK, KRAS + PD-1	Active clinical trials	Strategy to delay resistance

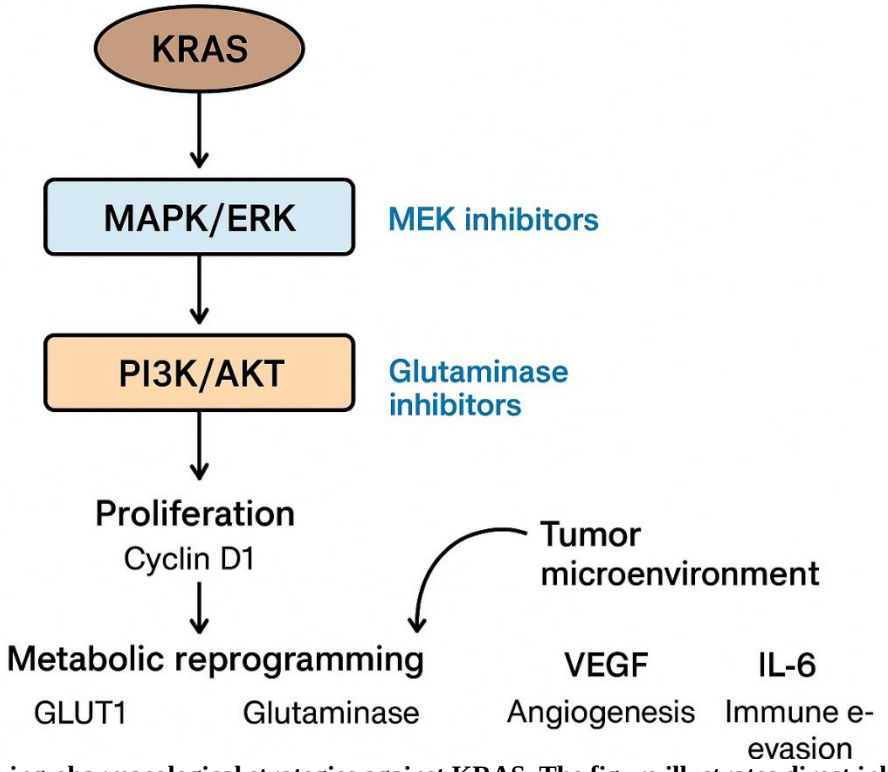

Figure 2: A schematic showing pharmacological strategies against KRAS. The figure illustrates direct inhibitors binding mutant KRAS (G12C, G12D), upstream inhibition via SHP2 and SOS1, downstream blockade through MEK/PI3K inhibition, RNA-based suppression at the transcript level, and targeted degradation through the proteasome pathway.

9. RESISTANCE MECHANISMS AND COUNTERSTRATEGIES

While the development of KRAS-targeted therapies, particularly G12C inhibitors, represents a breakthrough in precision oncology, therapeutic resistance remains a major limitation. Both primary resistance, where tumors fail to respond initially, and acquired resistance, where tumors relapse after an initial response, have been observed across cancer types [93]. Understanding these mechanisms is essential for designing rational counterstrategies to enh**10. Resistance to KRAS-Targeted Therapy**

10.1. Primary Resistance Primary resistance occurs when there is no clinical benefit despite a targetable KRAS mutation. Several factors contribute:

Tumor Heterogeneity: Co-mutations in TP53, STK11, or KEAP1 shape tumor biology, often leading to immune-cold phenotypes and poor responses to KRAS inhibitors or immunotherapy [94].

Bypass Signaling Pathways: Active EGFR, HER2, or FGFR pathways allow tumor cells to proliferate independently of KRAS [95].

Intrinsic Signaling Redundancy: Other RAS isoforms (NRAS, HRAS) or downstream kinases maintain signaling in KRAS-driven tumors [96].

10.2. Acquired Resistance Acquired resistance emerges after initial response to therapy, particularly with KRAS G12C inhibitors:

On-Target Mutations: Secondary KRAS mutations (e.g., Y96D, H95Q) disrupt drug binding [97].

Upstream Activation: Amplification of EGFR, MET, or HER2 restores downstream signaling [98].

Downstream Reactivation: BRAF, NRAS, or MEK mutations reactivate the MAPK pathway [99].

Phenotypic Transformation: Some lung cancers transform from adenocarcinoma to squamous or small cell carcinoma, altering therapeutic vulnerabilities [100].

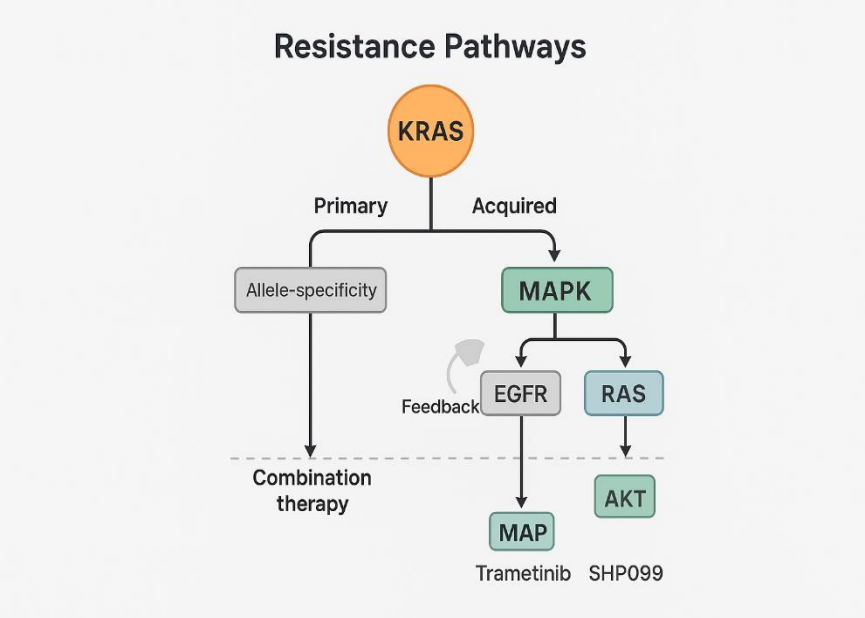

Figure 3: Mechanisms of resistance to KRAS-targeted therapy

10.3. Tumor Microenvironment The immunosuppressive microenvironment, driven by regulatory T cells, myeloid-derived suppressor cells, and cytokines like IL-6 or GM-CSF, contributes to resistance, reducing the efficacy of targeted

therapies and immunotherapy [101, 102].

10.4. Counterstrategies
Next-Generation Inhibitors: Targeting G12D, G12V, or pan-KRAS inhibitors to expand coverage [103].

Combination Therapies: Co-targeting EGFR, MET, MEK, or PI3K to suppress bypass pathways; trials show promise but toxicity is a concern [104, 105].

SHP2/SOS1 Inhibition: SHP2 (e.g., RMC-4630) or SOS1 (e.g., BI-1701963) inhibitors block upstream activators [106].

Immunotherapy Combinations: KRAS inhibition paired with checkpoint inhibitors to enhance immune response, though results are mixed [107].

Microenvironment Targeting: CSF1R or IL-1β inhibitors to reprogram the immunosuppressive milieu [108].

10.5. Clinical Implications Resistance necessitates dynamic monitoring via liquid biopsies to detect circulating tumor DNA and guide adaptive treatments [109]. Resistance mechanisms vary by tumor type, with EGFR-mediated bypass common in colorectal cancer and histologic transformation in lung cancer [110].

10. RESISTANCE MECHANISMS AND COUNTERSTRATEGIES

Resistance Mechanism	Example Findings	Potential Counterstrategies
On-target KRAS mutations	Y96D, H95Q disrupting G12C inhibitor binding	Next-generation inhibitors, pan-KRAS degraders
Upstream activation	EGFR, MET, HER2 amplification	KRAS inhibitor + EGFR/MET inhibitors
Downstream reactivation	NRAS, BRAF, MEK mutations	Dual KRAS + MEK or PI3K inhibition
Parallel pathway activation	PI3K–AKT signaling	Combination with PI3K/mTOR inhibitors
Phenotypic transformation	Adenocarcinoma → small cell carcinoma	Chemotherapy, histology-specific therapies
Tumor microenvironment	Tregs, MDSCs, IL-6 secretion	Checkpoint inhibitors, CSF1R blockade

11. CLINICAL AND PHARMACY IMPLICATIONS

12.1. Genomic Profiling KRAS mutation testing via tumor tissue or liquid biopsy guides therapy in NSCLC (sotorasib, adagrasib), colorectal cancer (trial eligibility), and pancreatic cancer (genotyping for trials) [112–114]. Pharmacists interpret genomic data and advise on therapy [115].

12.2. Approved Therapies Sotorasib and adagrasib are FDA-approved for KRAS G12C-mutant NSCLC; adagrasib shows activity in brain metastases and colorectal cancer trials [116, 117]. Pharmacists manage dosing, access, and adherence [118].

12.3. Adverse Events KRAS inhibitors cause gastrointestinal issues, hepatotoxicity (20–30% of patients), fatigue, and musculoskeletal pain, requiring monitoring and supportive care [119–121].

12.4. Drug Interactions Sotorasib and adagrasib, metabolized by CYP3A4, interact with CYP3A4 modifiers and proton pump inhibitors, necessitating careful management [122, 123].

12.5. Pharmacy in Trials Pharmacists support trial design, drug supply, and pharmacovigilance for combination therapies [124, 125].

12.6. Cost and Access High costs limit access; pharmacists advocate for reimbursement and support programs [126, 127].

12.7. Oncology Pharmacy Pharmacists require expertise in precision medicine, collaboration, education, adherence, and pharmacovigilance.

12. FUTURE DIRECTIONS AND CONCLUSION

14.1. Future Directions G12C inhibitors benefit a subset of patients, but broader strategies target G12D, G12V, and G13D

via allosteric inhibitors, RNA-based therapies (siRNA, mRNA vaccines), and PROTACs [87–89]. Combination therapies with MEK, ERK, PI3K, or immunotherapy counter resistance [90, 91]. Personalized medicine, using next-generation sequencing and liquid biopsies, tailors therapy [109]. Preclinical models like organoids and CRISPR-Cas9 aid drug development.

14.2. Conclusion KRAS drives NSCLC, colorectal, and pancreatic cancers. G12C inhibitors, emerging non-covalent inhibitors, RNA therapies, and PROTACs expand options. Combinations with MAPK/PI3K inhibitors or immunotherapy address resistance. Genomic profiling and liquid biopsies optimize outcomes. Future research should focus on variant-specific inhibitors and diverse trials to improve survival and quality of life.
ance treatment efficacy and durability.

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