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KRAS protein mutations in colorectal cancer: Molecular pathways and therapeutic opportunities

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Abstract
The mutations in the KRAS proteins are among the most crucial molecular events that contribute to the initiation and development of colorectal cancer (CRC). KRAS being a key part of the RAS/MAPK signaling cascade pathway, KRAS mutations (especially G12D, G12V, and G13D) lead to constitutive activation of downstream signaling pathways that mediate cell survival, cell proliferation, and cell differentiation. The changes enhance unregulated tumor progression, reorganization of metabolic activity, epithelial-mesenchymal transition (EMT), and resistance to targeted therapies, in particular, anti-EGFR monoclonal antibodies. Recent progress with high-resolution genomics further illuminated the various biological implications of specific KRAS alleles to show that individual sub-types of mutations possess specific oncogenic capabilities, and therapeutic weaknesses. Mutant KRAS also affects several networks, such as PI3K/AKT, RAF/MEK/ERK, RAL-GEF, and metabolic events that engage glycolysis and autophagy. Such interactions promote not only the aggressiveness of tumors but also an immunosuppressive microenvironment with a decrease of infiltration of cytotoxic T-cells and a corresponding increase of inflammatory cytokines secretion. Although historically KRAS has been classified as undruggable, allele-specific inhibitors, especially KRAS G12C inhibitors that take advantage of covalent interaction with the mutant cysteine site, have been achieved. Additionally, dual therapy with upstream agonists (EGFR, SHP2, SOS1) and downstream inhibitors (MEK, ERK) have demonstrated positive outcomes in preclinical and first line clinical trials. Therapy approaches are also developing and include synthetic lethality, immunotherapy repression, and metabolic therapy. The knowledge of the specific molecular implications of KRAS mutations provides a growing world of opportunities to treat patients with CRM personally and provide better outcomes.

Keywords: KRAS mutations, colorectal cancer, MAPK signaling pathway, Tumor microenvironment, Molecular mechanisms

1. Introduction
The second cause of cancer related deaths in the world is colorectal cancer (CRC). Even though more efficient screening and treatment methods have led to a significant decrease in the prognoses, there is still an urgent necessity to identify more specific treatment plans, especially in relation to CRC caused by KRAS oncogenic mutations. The process of colorectal carcinogenesis is usually marked by the loss of the tumor suppressor APC, which is then succeeded by mutations in KRAS, and finally by mutation in TP53 [1, 2].

KRAS gene is the most commonly mutated oncogene in CRC with mutations found in more than 45 percent of the cases. These mutations correlate with anti-epidermal growth factor receptor resistance and a low prognosis. Of the three codons that are a CRC hotspot (12, 13, 61), the most common codons to be substituted is codon 12 [3]. In addition, the systematic analysis of the changes that are linked to CRC and are predicted to be functional has found numerous alterations in either KRAS itself or downstream genes. Together, these changes modify a large portion of the CRC signaling circuitry that the upstream ERBB receptors interact with, and indicates a complete reprogramming of the disease [4].

Therapeutic strategies directed against KRAS-mutant CRC and avenues for further investigation have emerged as a result of a growing understanding of the genomic, transcriptomic, and proteomic networks activated by these lesions [5, 6].

2. Overview of KRAS Biology

KRAS (Kirsten rat sarcoma viral oncogene homolog) is a member of the RAS family of small GTP-binding proteins in humans and is essential for life [7]. The gene encodes an approximately 21-kDa protein that regulates cellular signal transduction by cycling between a GDP-bound inactive and a GTP-bound active state. KRAS is localized at the inner face of the plasma membrane, where it interacts with membrane anchor molecules to receive and transmit signals from cell surface receptors to numerous downstream effectors that mediate different biological functions, such as cell proliferation, differentiation, motility, and apoptosis. Mannich-like or Michael-type nucleophilic attack of the phosphate moiety of GTP by the side chains of aspartate (D) or glutamate (E) residues greatly accelerates the inherent GTPase activity of KRAS leading to GTP hydrolysis [8]. Upon hydrolysis, the protein returns to the inactive state, with subsequent release of inorganic phosphate (Pi). The KRAS gene has four key isoforms, with isoform recognition and nomenclature varying widely across species. In humans and mice, the gene consists of four exons, which encode a 188-amino-acid p21 protein [9]. KRAS mutations occur frequently in colorectal cancer (CRC), lung adenocarcinoma, and pancreatic cancer. The KRAS protein can code for four isoforms: KRas4A (also called KRas1A or K-Ras1), KRas4B (also called K-Ras2 or K-Ras), and N-Ras. Ras proteins are small GTPases and belong to the Ras superfamily of GTP-binding proteins. They regulate intracellular signal transduction pathways downstream of receptor tyrosine kinases (RTKs) [10]. Ras is commonly found in the membrane, where guanine nucleotide exchange factors (GEFs) catalyze the conversion of the inactive GDP-bound form (Ras-GDP) to the active GTP-bound form (Ras-GTP). Several factors, including the cytoplasmic domains of RTKs, have been identified as Ras-GEFs. When bound to GTP, Ras activates several downstream effectors signaling cascades, including the mitogen-activated protein kinase/extracellular regulated protein kinases (MAPK/ERK) cascade and the phosphoinositide 3-kinase (PI3K)/Akt pathway. KRAS also signals through coordinate's cross talk with various pathways. Upon GTP hydrolysis, Ras is converted back to its inactive form (Ras-GDP). GTP hydrolysis is intrinsically slow and is significantly accelerated by GTPase-activating proteins (GAPs). The specific enzymatic activities and cellular effects mediated by KRAS, NRAS, and HRAS are comparable and can partially overlap [11].

KRAS mutations often occur at codons 12, 13, and 61. Mutations at codons 12 and 13 occur in 98% of all KRAS mutations in CRC and G12D, G12V, and G13D are the most frequently observed subtypes in CRC. Codons 61 mutations activate specific downstream pathways and clinical response to targeted therapy. KRAS mutant CRC is resistant to therapy inhibiting epidermal growth factor receptor (EGFR) and its upstream signals, p53 mutations often co-occur with KRAS mutation, co-mutations in SMAD4, PIK3CA, TP53, and other genes act in parallel on TGF-β and MAPK pathway, hypoxia-inducible factor (HIF), NF-κB, NOTCH, and other pathways and cooperate with KRAS to increase malignant potential in CRCs studied and genomic, transcriptomic, and proteomic data indicate extensive crosstalk between KRAS and pathways regulated by co-mutations [12].

3. KRAS Mutations in Colorectal Cancer: Epidemiology and Spectrum

KRAS mutations occur in approximately 45% of colorectal cancer (CRC) cases and predict worse prognosis [13]. Colorectal cancer is the third most common cancer globally. It is the second most fatal neoplasia with two million new cases and one million deaths worldwide in 2020. The distribution of KRAS mutations differs according to population, tumor site, and the cancer's clinicopathologic stage. In codon 12, G12D occurs frequently and correlates with right-sided tumor location and multiple extra-colonic cancers. Codon 13 G13D is the most prevalent lesion in Stage I CRC. Codon 61 Q61H occurs in problems of the right colon, and R61 mutations associate with poor prognosis. Furthermore, KRAS mutations have been implicated in poor therapeutic response [14]. KRAS testing should be routinely performed by all laboratories, regardless of patients' previous therapies, according to the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) guidelines. Consensus mutations refer to those detected by FDA-cleared or CE-IVD-marked tests and are typically those at codons 12 and 13. In particular, manual re-evaluation of KRAS results may be warranted in cases of candidate therapies involving anti-EGFR treatment. For case selection and therapy decision criteria, testing for KRAS remains mandatory in advance stages, Figure 1 [15, 16].

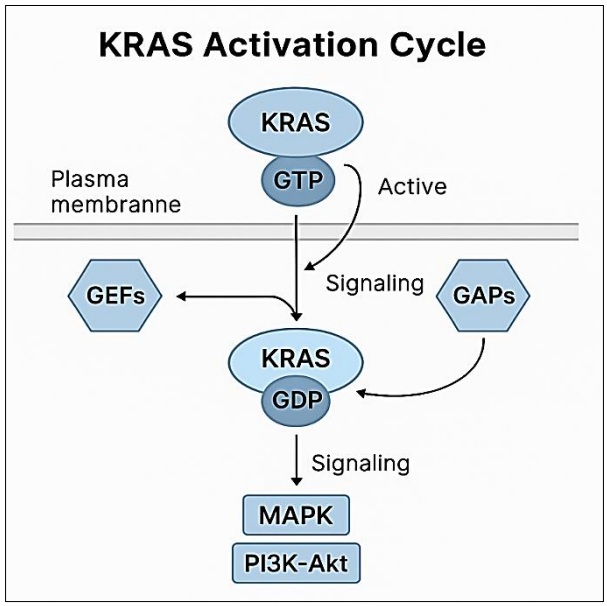

Fig 1: KRAS cycle in colorectal cancer

4. Molecular Pathways Driven by Mutant KRAS in Colorectal Carcinogenesis

Oncogenic KRAS mutations deeply rewire the colorectal cancer (CRC) signaling landscape, yet they do not influence tumor initiation when considered in isolation. In mice, KRASG13D school-initiated tumors retain faithful Wnt signaling and proliferate in 3D organoid culture using a medium that supports stem-cell-like behavior [17]. Examination of organoid growth advantages at different KRAS-generating locations demonstrated that mutations in codon 12, such as G12D, confer a significant boost to proliferation and fitness over other locations termed 'null' or 'nonhotspot' [18]. Co-occurring mutations at other loci, such as TP53 or SMAD4, do not further enhance KRAS-driven proliferation, Figure 2 [18].

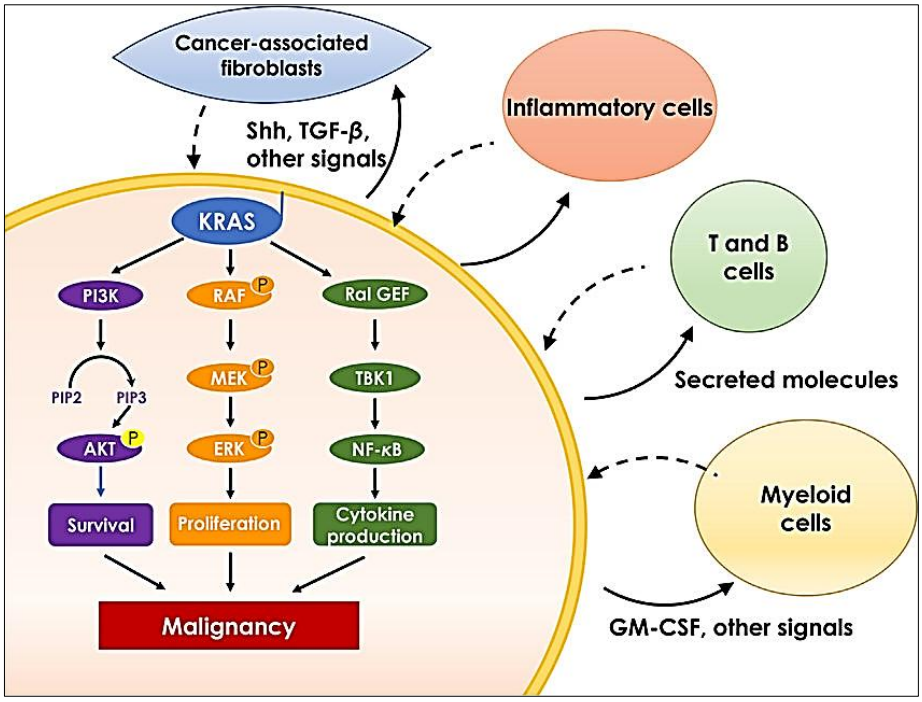

Fig 2: Molecular pathways of KRAS in colorectal

After KRASG13D Wnt-driven initiation, additional mutations such as TP53, PIK3CA or BRAF agonists are frequently acquired, but these are no longer essential for CRC development. Despite rigorous attempts, yet no specific therapeutic approaches targeting KRAS-mutated cancers have gained approval. Therefore, the available studies aim at defining accurately the complex pathways regulated by mutant KRAS. Oncogenic mutations in KRAS found in CRC cause extensive activation of mitogen-activated protein kinase (MAPK) and other complementary tumor signaling pathways that have a fundamental role in cellular behavior. The effector proteins are the RAF and phosphoinositide 3-kinase (PI3K) which are the main downstream intermediates of these integrated networks. These outputs of pathways are oncogenically tuned by oncogenic KRAS in the various multistage tumorigenesis processes. Moreover, KRAS mutations also increase receptor tyrosine kinase (RTK) interaction by different conduits (under some conditions), orchestrating cross-talk with other oncogenic signals and remaining able to co-operatively interact [18, 19].

5. Interaction with Other Oncogenic Alterations and Pathway Crosstalk

Mutant KRAS is often observed to have co-occurring genomic changes in colorectal cancer, mainly PIK3CA, TP53, and SMAD4. These interactions cause changes in downstream signaling pathways, reaction to directed treatment, and aftermath clinicopathologic conduct [20]. Mutations in PIK3CA and/or TP53 increase KRAS-mediated signaling via feedbacks, and loss of SMAD4 inhibits RAS-ERK axis response and stimulates compensatory re-modulation of RAS-PI3K signaling. Combined mutant KRAS-colorectal cancer analysis identified RAS downstream signaling signature enrichment in PIK3CA- or TP53 -co-mutated tumors but suppressed signaling alongside SMAD4 loss. The transcriptomic and combinatoric genomic studies show that KRAS and PIK3CA mutants strongly interact with each other at the protein, transcriptional and copy-number levels [21].

KRAS-driven tumors are the most adaptive and flexible to accommodate oncogenic changes with deleterious consequences on the RAS network. Proliferation continues unabated following pharmacologic or genetic inhibition of RAS or RAF, with restored signaling through alternative oncogenic nodes [8]. In these contexts, KRAS represents a non-essential, adaptive node rather than a primary, growth-promoting driver. These studies underscore the capability of KRAS-driven tumors to withstand perturbation by a selected repertoire of feedback-connected components, enabling sustained growth and amplifying intrinsic resistance to selective therapeutic pathways, Figure 3 [22, 23].

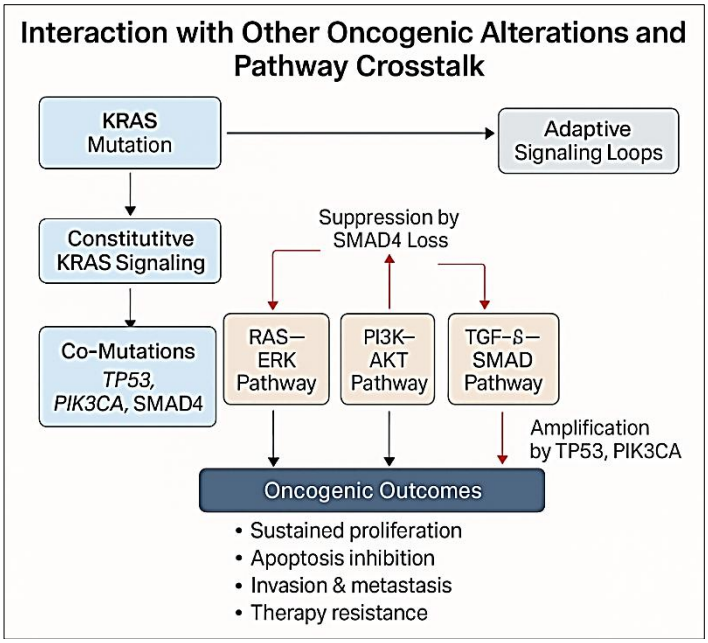

Fig 3: Oncogenic Crosstalk between KRAS Mutations and Co-Occurring Genetic Alterations in Colorectal Cancer

6. Clinical Implications of KRAS Status in Colorectal Cancer

In colorectal cancer (CRC), KRAS status is a key predictor of treatment response, especially to anti-EGFR therapies. Patients with KRAS mutations derive limited benefit from anti-EGFR monoclonal antibodies, a finding that has been well established in prospective trials [24]. In addition, co-mutations such as TP53 and PIK3CA have been linked to distinct chemoresistance patterns in CRC that are also KRAS-status dependent [24], raising the possibility that combination therapies targeting both mutant KRAS components and such co-alterations might be effective in the disease. Notably, although KRAS mutations are not universally required for proliferation of CRC cells or tumor-initiation following organoid implantation, in the absence of these mutations a more differentiated epithelium is observed, suggesting that a KRAS-altered state, despite being insufficient for proliferation, still exerts profound effects on differentiation that might be critical [25]. Understanding the specificity and scope of these KRAS-driven aspects might thus guide the development of strategies complementing targeted therapies and further enhance patient stratification. More generally, information on downstream effectors and co-occurring mutations is essential for delineating both the therapeutic potential and limitations of KRAS-inhibitors that have entered the clinic, and for identifying allosteric or indirect approaches capable of targeting mutant signaling effectively. Such insights might also complement a broader effort to define the KRAS "addiction" paradigm across cancer types [26, 27].

7. Therapeutic Strategies Targeting KRAS-Driven Colorectal Cancer

Mutant KRAS is the most prevalent oncogenic alteration in colorectal cancer, which occurs in approximately 40-45% of cases. The G12C mutant of KRAS is an actionable target in lung adenocarcinoma, and various small-molecule inhibitors of KRAS and downstream pathway modulators are being evaluated in phases I-III clinical trials for the treatment of colorectal cancer. Despite intense efforts in drug development, strategies targeting mutant KRAS remain largely unavailable [28]. In the past decade, interest in KRAS as a therapeutic target has resurfaced due to the discovery of small-molecule inhibitors that selectively target KRASG12C and inhibit KRAS signaling in preclinical models and patients with non-small-cell lung cancer (NSCLC). In the absence of direct inhibitors, efforts to target the downstream effector pathways have taken precedence [29].

Given the unique metabolic reprogramming associated with KRAS mutations and the identification of synthetic-lethal partners, targeting nutrient dependencies, coupling nutritional intervention with pharmacologic strategies, and seeking additional vulnerabilities from genome-scale screens should be prioritized. Because tumors with an oncogenic KRAS mutation exhibit distinct transcriptomic signatures for immune-related gene sets, further dissection of the immune landscape is anticipated to point toward new combination opportunities. Investment to develop robust evaluable biomarkers of response to any therapeutic regimen is essential [30].

7.1. Direct KRAS Inhibitors

KRAS-G12C inhibitors irreversibly lock the KRAS-G12C-GDP conformation and thus block nucleotide exchange. Aside from G12C, however, direct inhibitors exhibit little to no activity against other KRAS mutations. Despite early clinical promise in KRAS-G12C-mutant colorectal cancer, lung cancer, and other indications, direct inhibitors did not extend progression-free survival relative to standard chemotherapy [31, 32]. In KRAS-G12C-mutant colorectal cancer, these inhibitors induced high rates of resistance via KRAS reactivation, downstream pathway bypass, or multiple combination routes; resistance combinations conferring insensitivity to continuous KRAS-G12C inhibition also emerged [33, 34].

7.2. Upstream and Downstream Pathway Modulation

Mutant KRAS is a prerequisite for colorectal cancer (CRC) development, yet the therapeutic strategies targeting RAS directly or its structured-oriented downstream and upstream pathways are still being explored. Although preclinical

investigations revealed an increasing catalogue of direct KRAS inhibitors, very few of these have moved into clinical practice. Abundant studies already explored the rationale of targeting KRAS upstream and downstream pathways to attenuate RAS-driven signaling in CRC, whereas those criteria governing relevant combinations remain to be scrutinized. Furthermore, when and under what conditions such combined approaches are appropriately applied are far from being elucidated [35].

In the context of KRAS G12C mutation, the employment of potent ERK inhibitors appears to exert contrary effects depending on the administration time and that ERK inhibitors are beneficial when introduced after G12C inhibition [36]. In the meantime, the correlation of mitotic cultivated medium supplemented with serums together with MET amplification portending G12C inhibitors shows increased HGF and subsequent MET phosphorylation strengthens at the downstream of the RAS signaling pathway indicating an alternative route to potentiate signal transduction. The anti-tumor effect of Pan-RAF inhibitors remains enigmatic upon KRAS mutation existing when stimulating the MAPK pathway through growth factors. It suggests these agents have contradictive roles in distinct cellular conditions during G12C abrogation which warrants further investigation [37, 38].

Targeting the PI3K pathway in KRAS-driven tumors enables perturbed PI3K-AKT activity followed by attenuation of relevant cancer hallmarks which demonstrates efficacy alone or in combination with MEK inhibitors observing considerable therapeutic synergetic effect. Consequently, over-acquisition of such benefit contextually hints that restricting G1S cell cycle transition at early stage promotes adaptive metabolic changes propelling rapid cell proliferation to restore PI3K-AKT drive [39]. Moreover, in the presence of serums elaborating PIK3CA mutations across diverse tumors when KRAS-driven CRC or thyroid cancer endorse G12D facilitates adaptive PI3K pathway signification vigor under MET stimulation [40, 41].

The therapeutic landscape of CRC has been extremely challenged by the introduction of targeted anti-EGFR monoclonal Abs, nevertheless still restricted to the ‘classic’ oncogenic RAS/BRAF mutations [42, 43]. Extensive comprehension of aberrant signal transduction links to sophisticated alteration of metabolic patterns invokes flexible modulation use of large pool of historically neglected agents either alone or in drug cocktail formation. Since altered gene expression persists in the actively selected population clustering around RAS pathways observing no mutation hence onwards, provides additional insight to further interrogate pre-clinical possibility of cutting-edge target on routinely clinical undesirable signaling proportion binding to the broader most deleterious genetic counterpart, Figure 4 [44, 45].

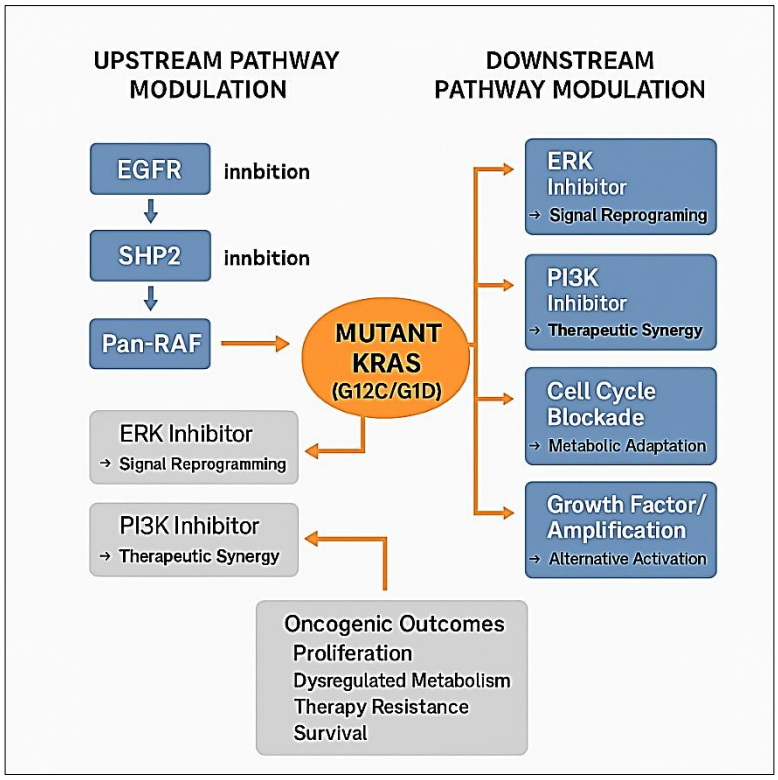

Fig 4: Therapeutic Targeting of Upstream and Downstream Pathways in KRAS-Mutant CRC

7.3. Synthetic Lethality and Metabolic Targeting

Oncogenic KRAS mutations impose metabolic burdens on neoplastic cells while triggering compensatory reprogramming [46, 47]. Such vulnerabilities have motivated extensive synthetic-lethal exploration and identification of nutrient dependencies [47]. Synthetic-lethal partners of the KRAS-driven condition provide candidates for combinatorial strategies; loss of additional genes such as BCL-X, CDK4, or STK33 confers further selectivity in various contexts. Nutritional constraints, cell-death-promoting co-treatments, and metabolic pathway-specific agents that complement concerted nutrient withdrawal also arise as promising options [48].

Mutant KRAS colorectal models expose dependencies on serine and glutamine, as well as on glycine under specific conditions. Integrated screening has highlighted the pivotal role of serine synthesis and utilization [49]. Residue-level dependencies have narrowed to G12D within mutant

contexts. Combinatorial strategies with therapeutic potential include glutamine-targeted treatments and co-inhibition of THRSP or other core nodes of the requisite serine network, which display coregulated expression with the KRAS genotype [50, 51].

7.4. Immunotherapeutic Considerations in KRAS-Mutant Disease

Antigenic modulation of KRAS mutant neoplasms appears questionable, given the biophysical properties of DE and residual oncofetal polypeptides expressed aberrantly in cell lines harboring KRAS mutations. There is ample evidence, however, implicating immune evasion in neoplasia driven by mutant KRAS [52]. KRAS mutations mediate immune suppression in PDAC. The tumor microenvironment of KRAS mutant neoplasms fosters a CD8+ T-cell exclusion pattern characterized by markedly reduced intratumorally CD8+ T-cell density and negligible PD-1 expression. This pattern is consistent with immunological profiling of KRAS mutant colon cancer cell lines decomposed on gene set variation analysis to identify clusters of tumor cells that preferentially foster T-cell exclusion. Ex vivo enrichment of CD8+ T-cells in the presence of TGF-β inhibits CD8+ T-cell proliferation and IFNγ production, and upregulates immune checkpoints [17]. High expression of the SMAD6 TGF-β antagonist and loss of activity of the concomitant TGF-β RII co-receptor is associated with improved survival in colon cancer [53, 54].

Tumoral infiltrates of CD4+ and CD8+ T-lymphocytes are more abundant in mutant KRAS than wild-type colorectal neoplasms; nevertheless, most remain unsupervised and no correlation is found with PD-L1 expression [55]. Similar high densities of CD4+ and CD8+ T-cells mark either KRAS mutant or wild-type non-small cell lung cancer (NSCLC). While mutant KRAS in a cohort of early-stage KRAS+ colorectal cancers were found to associate with larger T-cell responses, KRAS codon-12-G12D-or-13-R mutation status in patients with a diverse panel of an early-stage cancers failed to correlate with TMB or neoantigen load in a larger study. Thus, KRAS mutation status does not intrinsically predict anti-PD-1/PD-L1 response, but TMB serves as a useful surrogate biomarker and has been used to investigate combination approaches. Among the agents under examination are anti-CTLA-4, anti-PD-1, anti-PD-L1 monoclonal antibodies, and multivalent neoantigen vaccines towards various cancers, TABLE 6 [56].

8. Challenges, Resistance Mechanisms, and Biomarker Development

The development of effective therapeutic strategies directed against mutant KRAS remains hampered by the emergence of resistance to pathway-targeted and direct KRAS-targeted therapies [57]. Primary and acquired resistance arises from various mechanisms, complicating treatment approaches [58]. Successful therapeutic strategies thus require reliable biomarkers to predict, monitor, and circumvent resistance [59]. Preclinical modeling of CRC remains challenging, and the limited transferability of findings from model systems has hampered the progress of rational drug discovery and the emergence of targeted therapies.

Mechanisms underlying primary resistance to direct inhibition of KRAS involve activation of the phosphoinositide 3-kinase (PI3K) pathway, pathway bypass through gain-of-function mutations in the downstream effectors BRAF or NRAS, the presence of KRAS G13D mutations, cyclin D1 overexpression, co-occurring loss-of-function mutations in the Hippo pathway, or amplification of the human epidermal growth factor receptor 2 (HER2) or other receptor ty80fb45c2-c238-4f72-a28b-b1b0f38719beine kinases (RTKs) [60]. Following initial response to KRAS G12C inhibition, a multitude of resistance mechanisms have been documented, including KRAS G12D mutations, highly heterogeneous amplification of the wild-type KRAS allele, mutation or amplification of BRAF, aberrations leading to extracellular signal-regulated kinase (ERK) reactivation through receptor or downstream signaling, histological transformation to squamous cell carcinoma, acquisition of humoral immunity and paracrine signals to promote KRAS-independent growth, and factor-inducible loss of XIAP expression. Resurgence of extracellular signal-regulated kinase (ERK) activation subsequent to KRAS G12C inhibition, for example, is frequently mediated by secondary mutations in EGFR or genes encoding other RTKs, PI3K, and MAPK pathway effectors [61].

Biomarkers proposed to associate with resistance to KRAS-targeted therapies in CRC exhibit broadly heterogeneous profiles among different cancer types. Variants prioritized for clinical investigation include amplification of RTKs such as HER2 and mutations or epigenetic silencing of DUSP4, KSR1, and other MEK-target upstream negative regulators of receptor-extracellular signal-regulated kinase-extracellular signal-regulated kinase signaling [62, 63].

9. Future Directions in Research and Therapy

The future landscape of KRAS-directed therapy holds promise, guided by ongoing efforts to delineate resistance mechanisms. Combining KRAS inhibitors with downstream pathway inhibitors, immunotherapeutic, or standard-of-care chemotherapy warrants further investigation. Tumor stratification based on the heterogeneity and subtypes of KRAS mutations will be crucial for optimizing patient selection and therapy efficacy. Advances in understanding KRAS mutants enable the development of increasingly effective, targeted treatments [64].

Several innovative therapeutic modalities are being pursued to engage the KRAS GTPase, including covalent small-molecule inhibitors that directly target the activated KRASG12C mutant, PROTACs designed to facilitate selective degradation of oncogenic KRAS, and allosteric inhibitors that sequester KRAS away from effectors without affecting GTP hydrolysis. Integration of profile-matched KRAS pathway inhibitors, multiplexed PK/PD analyses of preclinical models, and real-time reporting of downstream signaling may enhance the design of clinical trials in KRAS-mutant malignancies [65].

10. Conclusion

Clinical and preclinical evidence supports a prominent role for mutant KRAS in colorectal tumorigenesis and suggests substantial opportunities for therapeutic intervention. The specter of KRAS-driven colorectal cancer thus emerges as a prime candidate for accelerated investigation and development toward personalized therapy

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Declaration of Competing Interest

The authors say they don't have any known personal or financial relationships or financial interests that could have seemed to affect the work in this study.

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