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Targeting KRAS in pancreatic cancer: new drugs on the horizon

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Abstract

Kirsten Rat Sarcoma (KRAS) is a master oncogene involved in cellular proliferation and survival and is the most commonly mutated oncogene in all cancers. Activating KRAS mutations are present in over 90% of pancreatic ductal adenocarcinoma (PDAC) cases and are implicated in tumor initiation and progression. Although KRAS is a critical oncogene, and therefore an important therapeutic target, its therapeutic inhibition has been very challenging, and only recently specific mutant KRAS inhibitors have been discovered. In this review, we discuss the activation of KRAS signaling and the role of mutant KRAS in PDAC development. KRAS has long been considered undruggable, and many drug discovery efforts which focused on indirect targeting have been unsuccessful. We discuss the various efforts for therapeutic targeting of KRAS. Further, we explore the reasons behind these obstacles, novel successful approaches to target mutant KRAS including G12C mutation as well as the mechanisms of resistance.

Keywords

KRAS; Pancreatic cancer; KRASG12C; KRAS inhibitor; KRASG12C inhibitors; PROTAC; KRAS vaccine

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the most common type of pancreatic cancer. It is the 4th most common cause of cancer-related mortality in the USA with over 45,000 estimated deaths each year, and a consistently rising incidence rate [1–3]. PDAC remains one of the most recalcitrant malignancies with an overall 5-year survival rate of only 10%, which is the lowest among all cancers [3]. Diagnosis at a late stage, when the tumor had already metastasized, and the limited therapeutic options contribute to this poor prognosis [2].

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The four most common genetic alterations in PDAC are activating mutations in *KRAS* and inactivating mutations in *CDKN2A*, *TP53*, and *SMAD4* [4–6]. In 2016, Bailey et al. performed integrated genomic analysis of 456 PDAC samples and found 4 molecular subtypes including squamous, pancreatic progenitor, immunogenic, and aberrantly differentiated endocrine exocrine (ADEX). The ADEX PDAC was shown to activate KRAS. Overall, the recurrently mutated genes were found to aggregate in several pathways including KRAS, G1-S cell cycle checkpoint, TGF-β, and WNT [7]. *KRAS* is the most commonly mutated oncogene in pancreatic cancer, found in over 95% of cases, and in approximately 90% of PDAC cases in particular, and is considered a master oncogene that regulates several cellular proliferation and survival pathways [4, 7]. Therefore, KRAS has been considered as the ultimate target for PDAC therapy. To date, several attempts have been made to target KRAS, most of which have been unsuccessful, which highlighted that it is notoriously difficult to target, and it was considered undruggable for a long time [8, 9]. There are several reasons behind this difficulty in drugging KRAS. First of all, GTP competitive inhibitors could not be developed due to the high affinity of KRAS for GTP in the picomolar range, whilst GTP is ubiquitously present in the cell in the sub-millimolar range, making competitive inhibition thermodynamically unfavorable [10, 11]. Other than the nucleotide binding pocket, no allosteric regulatory pocket and no other deep hydrophobic pockets were identified that were suitable for small molecule inhibitor development [12]. Nonetheless, the mutant KRAS G12C was successfully targeted recently, using mutant-specific covalent inhibitors that bind a novel allosteric pocket [13], which resulted in the FDA approval of KRAS G12C specific inhibitor AMG-510 (sotorasib). Although still challenging, perhaps it is now possible to view KRAS as a potentially druggable target.

In this review, we describe the different research efforts and the various strategies to target KRAS in PDAC. We discuss KRAS signaling and the role of KRAS in pancreatic cancer. Then, we discuss challenges and previous failed efforts to develop therapies to target KRAS and its pathways. Next, we examine some of the new and emerging therapeutics that target KRAS both directly and indirectly, including the new mutant specific KRAS G12C inhibitors, and recent efforts to target other KRAS mutants that are of interest for pancreatic cancer. We discuss several new therapeutics both in clinical and preclinical development, and promising emerging targeted therapy combinations. Finally, we discuss mechanisms of resistance that are associated with inhibiting KRAS signaling.

2. KRAS mutations in pancreatic cancer

2.1 KRAS signaling

The rat sarcoma (*RAS*) family of genes, comprising Kirsten RAS (*KRAS*), Harvey RAS (*HRAS*), and neuroblastoma RAS (*NRAS*), are frequently mutated in cancer [14]. The *KRAS* gene encodes a small GTPase protein that functions as a molecular switch for critical intracellular signaling pathways. KRAS cycles between an inactive GDP-bound state and an active GTP-bound state. In quiescent cells, KRAS is predominantly found in the inactive GDP-bound state. Upon activation of cellular transmembrane receptors such as EGFR by an extracellular signal, GDP is exchanged for GTP, resulting in KRAS activation and

propagation of the signal through downstream effector pathways (Fig. 1). This exchange is facilitated by guanine nucleotide exchange factors (GEF)s, whereas intrinsic KRAS GTP hydrolysis is accelerated by GTPase activating proteins (GAPs). GEFs and GAPs tightly control KRAS cycling in normal cells, where GEFs ensure GTP exchange only in the presence of extracellular stimuli and GAPs ensure fast GTP hydrolysis and return to the inactive state [15, 16]. GTP-bound KRAS can activate a myriad of downstream effector pathways, including RAF/MAPK and PI3k/AKT signaling pathways, which results in cellular growth, proliferation, and survival.

2.2 KRAS mutations

Mutant forms of KRAS have an impaired ability to hydrolyze GTP, resulting in an aberrant hyperactive state that activates downstream signaling pathways leading to increased cellular proliferation [17]. Activating *KRAS* mutations are considered a major driver of pancreatic ductal adenocarcinoma (PDAC). A point mutation in codon 12 of the *KRAS* oncogene is the most frequent mutation and is found in the majority of PDAC cases [5, 14]. This mutation results in a single amino acid substitution of glycine by aspartic acid in G12D mutations (45%), valine in G12V mutations (35%), arginine in G12R mutations (17%), alanine in G12A mutations, or cysteine is G12C mutations [18]. These missense mutations inhibit the ability of GAPs to accelerate GTP hydrolysis, resulting in excessive activation of KRAS [19]. Less frequent mutations include G13, Q61, K117, and A146. Despite progress in targeting KRAS G12C, these mutations represent a minority of KRAS mutations in PDAC. The major driver mutations in PDAC are G12D and G12V which collectively account for approximately 80–90% of KRAS driver mutations in PDAC [20]. Therefore, targeting these mutations has the potential of having a significant impact on PDAC therapeutics.

Oncogenic KRAS activation is influenced by the specific mutation and the presence of extracellular stimuli. Studies have shown that mutant KRAS undergoes rapid nucleotide cycling [21, 22] and requires activation by upstream signals for prolonged activation of KRAS and enhanced downstream signaling [21, 23, 24], supporting that KRAS is not locked in a static active state, and its activation is modulated by upstream signaling. Interestingly, biochemical profiling of the different mutant KRAS forms revealed intrinsic differences in the kinetics and biochemical properties between them [25]. Intrinsic GTP hydrolysis activity in the mutant forms differs according to the specific point mutation. Among G12 mutants, G12C, G12D, G13D mutant forms have high intrinsic GTPase activity, whereas G12A, G12R, G12V mutants have a low intrinsic GTP hydrolysis rate [25]. Mutants also differ in their sensitivity to GAP-mediated GTP hydrolysis and affinity for RAF kinase. Moreover, studies have shown that different KRAS mutations result in biological differences in downstream pathway activation in the tumor and in response to therapy [26–28]. Studies have also demonstrated that different KRAS mutations could be associated with prognosis and different disease outcomes in pancreatic cancer [28–31]. This implies that the specific KRAS mutations possibly have a variable impact on tumor biology. These biochemical and physiological differences may have implications on which approach would be more suitable to target the various KRAS mutant forms.

Several critical downstream effector pathways are activated by oncogenic KRAS signaling. The three major effector pathways are the RAF-MEK-ERK MAPK pathway, PI3K-AKT-mTOR pathway, and the Ral guanine nucleotide exchange factor (RalGEF) pathway. These pathways have been the target of intense drug development research for various types of cancer, as they are commonly deregulated in various malignancies either by upstream mutations such as RAS or receptor tyrosine kinases (RTKs), or activating mutations of proteins within these pathways [32–34]. KRAS and downstream effector pathways regulate several cellular processes in pancreatic cancer. There is a plethora of evidence that mutant KRAS signaling is involved in promoting cellular growth, proliferation, survival, and metastasis. More recently, accumulating evidence is showing that KRAS mutations are associated with the regulation of diverse cellular processes in pancreatic cancer including autophagy, macropinocytosis, metabolic perturbations, and modulation of the tumor microenvironment [35–40].

3. KRAS in pancreatic cancer

3.1 Role of KRAS in pancreatic cancer development and subsistence

PDAC is thought to progress through a multistage process, where premalignant lesions accumulate mutations as they progress into malignant invasive carcinoma [41]. These lesions are known as pancreatic intraepithelial neoplasia (PanINs) and are classified according to the degree of cellular dysplasia from PanIN1 to PanIN3. KRAS mutations are found at the earliest stage of PDAC development (PanIN1) [42], suggesting that it is important for tumor initiation, and additional mutations in other genes are required for tumor progression. Several transgenic and genetically engineered mouse models (GEMMs) have been used to elucidate the role of mutant KRAS in PDAC initiation and progression [43–45]. The multistage development of PanIN lesions into invasive cancer has been recapitulated in the transgenic KRAS G12D mouse model [43, 44]. In those studies, all of the transgenic mice develop PanIN lesions, but only a subset of the animals develop invasive disease. These results show that mutant KRAS drives cancer initiation, but acquisition of further mutations is required for progression. Studies in GEMMs also explored whether mutant KRAS signaling is still required at later stages of tumor development, well after initiation [46–48]. An inducible mutant KRAS model has been developed, where KRAS G12D expression can be reversibly induced in the pancreata of mice. In this model, turning off oncogenic KRAS expression in established pancreatic and metastatic tumors resulted in tumor regression [46–48]. Collectively, these studies have shown that KRAS oncogenic signaling is critical for both initiation and maintenance of pancreatic cancer; therefore, it is the ideal target for therapy.

3.2 Role of KRAS in pancreatic microenvironment and metastasis

Pancreatic cancer has a dense fibrotic stroma which is composed of various different components including the extra cellular matrix (ECM), cancer associated fibroblasts (CAFs), the vasculature, and immune cells and has been shown to have a dichotomous role that can be pro-tumorigenic or anti-tumorigenic [49–51]. Oncogenic KRAS is implicated in the regulation of the tumor microenvironment (TME) and the recruitment of pro-tumorigenic cells resulting in tumor invasion and metastasis [40, 52]. CAFs are the major cell type

within the pancreatic cancer stroma, and evidence shows they have the capacity to promote tumor growth and progression. On the other hand, pancreatic tumor cells secrete a variety of factors and proteins that can activate and alter the function of CAFs and other cells in the TME. The hedgehog signaling pathway has been identified as a critical regulator of pancreatic cancer initiation and maintenance [53]. Pancreatic tumor cells secrete hedgehog ligand, which acts on nearby CAFs promoting a desmoplastic response [54, 55]. The role of hedgehog pathway in pancreatic cancer remains controversial and has been shown to have a dichotomous dose-dependent response that could either promote or inhibit tumor growth [56]. Recently, mutant KRAS has been shown to be involved in the activation of paracrine hedgehog signaling, and the promotion of reciprocal signaling between pancreatic tumor cells and the stroma [57]. In a proteomic and phosphoproteomic approach, it was found that KRAS G12D mutated tumor cells secrete sonic hedgehog, which activates pancreatic stellate cells, which are a subtype of CAFs, resulting in widespread alterations in the stellate cells, which in turn secrete growth factors that promote the desmoplastic response and also signal back to the tumor cells [57].

In addition to governing this crosstalk between tumor cells and CAFs, oncogenic KRAS has been implicated in regulating the immune microenvironment by promoting inflammation and immune evasion [40, 52]. KRAS mutations have been correlated with low immune cell infiltration in PDAC which is associated with a poorer prognosis [58]. Mechanisms controlling this immune evasion are not completely understood, but are likely to involve crosstalk between multiple cells including KRAS-driven tumor cells, CAFs, myeloid derived tumor suppressor cells, and tumor associated macrophages [59]. In a study using a pancreatic cancer syngeneic mouse model, KRAS knockout (KO) or KRAS G12D pancreatic tumor cells were injected into the pancreata of mice and monitored for tumor growth. Mice injected with KRAS KO cells rejected the cells or only grew tumors after a long latency period and were highly infiltrated by B and T lymphocytes, whereas cells with oncogenic KRAS grew rapidly, were able to evade immune regulation, and lacked B and T cell infiltration [60], suggesting a direct role for KRAS activation in promoting an immune-evasive microenvironment. Additionally, direct targeting of KRAS using G12C specific inhibitors has been shown to alter the immune microenvironment by increasing the infiltration of immune cells including CD8+ T-cells, increasing cytokine signaling, and antigen presentation [61, 62]. Taken together, these data demonstrate the essential role of KRAS in maintaining an immunosuppressive TME and an opportunity to combine KRAS targeting with immunotherapy for sustained responses to therapy.

4. Challenges in Kras targeted therapy in PDAC

4.1 Targeting KRAS directly

KRAS is a critical oncogene in over 80–90% of PDAC cases; therefore, it is a prime target in these oncogene addicted tumors. Significant research efforts have been focused on targeting KRAS both directly and indirectly (Fig. 1). Despite this, KRAS remains an elusive target in pancreatic cancer as various targeted therapies have failed to elicit sufficient clinical benefit. As previously mentioned, the structure of the KRAS protein lacking deep hydrophobic pockets, and its high affinity to GTP, prevented the development of effective

KRAS inhibitors. Recently, mutant KRAS inhibitors have been developed which will be discussed later in this review.

Due to difficulties in drugging KRAS directly, researchers investigated various methods of indirect targeting (Table 1). These efforts have focused on abrogating KRAS signaling through inhibiting its activation, or its downstream pathways. Post-translational prenylation of KRAS, which is catalyzed by farnesyl transferases (FTases), is required for its membrane localization and consequently signal transduction [63, 64]. FTase inhibitors (FTIs) have been designed to target KRAS farnesylation aiming to prevent its membrane localization, thereby preventing its activation, and some have been clinically investigated, including drugs such as lonafarnib and tipifarnib [65–67]. Despite initial excitement about FTase inhibitors for KRAS mutant PDAC, some of which progressed to phase III clinical trials for various cancer types, results in PDAC have been disappointing eventually [68–70]. In the presence of FTIs, KRAS was alternatively prenylated by geranylgeranyl transferase 1 (GGTase1) and targeted to the plasma membrane [71–73]. This showed that KRAS mutant tumors have the intrinsic ability to resist FTI therapy by alternative prenylation. A potential approach to combat this resistance is the dual inhibition of FTase and GGTase1 activity [74]. However, these approaches have a limited therapeutic window as GGTase 1 inhibitors have wide ranging targets.

4.2 Targeting KRAS downstream effector pathways

The RAF-MEK-ERK MAPK pathway is one of the best characterized pathways downstream from KRAS, and it has been intensively studied as a therapeutic target for KRAS mutant tumors [75]. Active KRAS induces the phosphorylation and dimerization of RAF, thereby activating it. Consequently, RAF phosphorylates MEK1 and MEK2, which in turn phosphorylate ERK1 and ERK2 [76]. ERK subsequently activates transcription factors that promote cellular proliferation. The activation of this MAPK pathway downstream of KRAS is critical for its oncogenic signaling. Several RAF, MEK, and ERK inhibitors have been developed, and some have been clinically studied in PDAC. RAF inhibitors vemurafenib and dabrafenib have been successful for the treatment of *BRAF* mutated tumors but failed in *KRAS*-mutant cancers. Both vemurafenib and dabrafenib resulted in the paradoxical transactivation of RAF dimers in *BRAF*-wild type *KRAS*-mutant cancers and therefore resulted in the propagation rather than the suppression of downstream signaling [77–80]. Pan-RAF inhibitors that target both monomers and dimers of RAF could potentially overcome its paradoxical activation [81].

The PI3K-AKT-mTOR pathway, which can be activated by KRAS signaling, has also been the center of multiple drug development efforts as it is involved in various cancers [33]. There are three classes of PI3Ks in the human cell. GTP-bound KRAS activates Class I PI3Ks, which in turn recruit AKT to the plasma membrane, resulting in the activation of mTOR. Several AKT substrates are involved in the regulation of diverse functions such as cellular growth, proliferation, survival, and metabolism [82]. The PI3K-AKT-mTOR pathway is upregulated in pancreatic neuroendocrine tumors (PNETs) [83]. The mTOR inhibitor everolimus showed benefit for patients with PNETs in a phase III clinical trial, resulting in its FDA approval for advanced PNETs [84]. However, PI3K pathway inhibitors

failed as single agents in PDAC [85, 86], possibly because of interconnected signaling pathways downstream of KRAS which could be alternatively activated upon the inhibition of one pathway. Therefore, targeting both PI3K and MAPK pathways has emerged as a potential therapeutic strategy [87, 88]. Preclinical results have shown strong synergy between inhibitors targeting the two pathways. Clinical trials however have not been successful in translating those results so far.

5. New and emerging strategies for targeting KRAS

5.1 Mutation-specific direct targeting of KRAS

Efforts to target KRAS directly have resulted in the development of KRAS G12C mutant-selective small molecule inhibitors [8, 13, 21, 22, 61, 89–91]. Using X-ray crystallography and mass spectrometry, Shokat and colleagues identified the druggable switch-II pocket in KRAS G12C where covalent small molecule inhibitors can bind [13]. They developed a series of compounds that irreversibly bind this pocket resulting in the disruption of switch-I and switch-II regions of KRAS making the GDP-bound state more favorable. These inhibitors effectively lock KRAS in the inactive GDP-bound state, preventing its binding to RAF and the activation of downstream signaling pathways. The reactivity of the cysteine found in KRAS G12C, which is a result of the missense mutation in codon 12, allows it to be exploited for the development of covalent small molecule inhibitors [92]. Since these inhibitors specifically bind the cysteine in the mutant form, they are mutant-specific and are expected to spare wild-type cells that lack this mutation, thereby reducing off-target toxicities.

Subsequent drug discovery efforts by multiple groups resulted in the development of several more potent covalent inhibitors of KRAS (G12C), including sotorasib, adagrasib (MRTX849), JNJ-74699157, and LY3499446, which rapidly moved into clinical investigation. Sotorasib has shown promising results in a clinical trial (NCT03600883) and has been given accelerated approval by the FDA in May 2021 for non-small cell lung cancer (NSCLC) [93]. Results from a phase II clinical trial of sotorasib in previously treated NSCLC (NCT03600883) have been recently reported [94]. The results are promising with 37.1% of the patients achieving an overall objective response (ORR), disease control (DCR) achieved in 80.6% of patients, and a median progression free survival of 6.8 months. A phase III trial is currently underway (NCT04303780). However, sotorasib has not been extensively examined in patients with pancreatic cancer.

MRTX849 is currently in clinical trials for patients with KRAS G12C mutant cancers, including pancreatic (NCT03785249). In phase I and II clinical trials, NSCLC patients achieved 45% objective response rate (ORR) and 96% disease control rate (DCR). The compound is currently in phase III clinical trial for NSCLC (NCT04685135) and colorectal cancer patients (NCT04793958). In preclinical studies, MRTX849 showed potent inhibition of cellular proliferation in a pancreatic cancer cell line [95]. One patient with pancreatic cancer has been reported to have a confirmed partial response in the phase I/Ib cohort (NCT03785249).

Another G12C inhibitor, LY3499446, was being investigated in a phase I clinical trial (NCT04165031). Despite promising preclinical results, the clinical trial has been terminated due to toxicities. Additional KRAS G12C inhibitors are in clinical trials including JNJ-74699157, GDC 6036, and D-1553. Details about these inhibitors have not been published, and data from ongoing clinical trials have not been reported.

KRAS G12C is the predominant KRAS mutation in NSCLC and is associated with tobacco mutation signatures [96]. However, G12D is the most prevalent KRAS mutation in PDAC, and only a small subset of patients harbors the G12C mutation. Therefore, most PDAC patients cannot derive benefit from these new inhibitors. Nonetheless, efforts to target KRAS G12D are underway. Various groups are working on developing new approaches and lead compounds to target GTP-bound KRAS G12D. A cyclic peptide, KD2, can selectively target GTP-bound KRAS G12D and has been shown to have the ability to access and bind the switch-II groove in mutant KRAS [97]. This shows that it is possible to drug GTP-bound KRAS G12D, but these cyclic peptides do not readily enter the cell, and further development of more drug-like compounds is required [98]. A bicyclic peptide called KS-58 showed activity against KRAS G12D mutated pancreatic cancer both *in vitro* and *in vivo* [99]. These studies provide proof-of-concept evidence that KRAS G12D mutation could be potentially targeted, which would benefit a larger number of PDAC patients. A small molecule inhibitor of mutant KRAS G12D called MRTX1133 is reported to selectively target the G12D mutant form of KRAS and result in regression of tumors harboring the mutation [100]. This drug candidate is in preclinical development, and details have not been published.

A new class of KRAS small molecule inhibitors, termed tricomplex inhibitors, that target the GTP-bound form of specific KRAS mutants is being developed (Fig. 2). These inhibitors bind in a novel pocket that is formed between the target mutant KRAS and a chaperone protein, cyclophilin A [101], thereby overcoming the challenge of finding a suitable pocket for inhibitors in KRAS. When tricomplex inhibitors enter the cell, they associate with Cyclophilin A, which is ubiquitous in the cell, forming a bi-complex, which then binds to KRAS via protein-protein surface interaction, resulting in the tricomplex [101]. The association of the chaperone with KRAS physically prevents it from binding to downstream effector proteins, thus blocking further signal transduction. The inhibitor RM-018, which is a prototype of G12C tricomplex inhibitors, is active against KRAS G12C mutated cancer cells that are resistant to other mutant-specific inhibitors [101]. A closely related tricomplex inhibitor of the GTP-bound active KRAS G12C, RMC-6291, is in preclinical development and on track to go to clinical trials. Additionally, a tricomplex multi-RAS inhibitor, RMC-6236, which can target multiple different mutations of KRAS, including KRAS G12V and different forms of RAS is also being developed [98]. Details of these inhibitors and their activity have not been published.

5.2 Non-mutation specific inhibitors

5.2.1 SOS1 interaction inhibition—Son of Sevenless (SOS1) is a guanine nucleotide exchange factor (GEF) that acts as an activator of KRAS[16]. SOS1 binds GDP-bound KRAS and catalyzes the exchange of GDP for GTP. SOS1 is critical for the regulation of KRAS signaling, and its depletion results in reduced cellular proliferation [102].

Therefore, the binding of SOS1 to KRAS emerged as a potential therapeutic strategy to target KRAS. Several molecules that block the interaction between SOS1 and KRAS have been developed [103, 104]. BI-3406 is a potent SOS1 inhibitor that is orally bioavailable, with anti-proliferative activity against cells harboring various KRAS mutations, but not on KRAS wild-type cells [105]. BI-3406 was shown to inhibit cellular proliferation and KRAS downstream signaling, and was synergistic with MEK inhibitors [105]. BI-1701963 is a SOS1 inhibitor derived from BI-3406, which is currently being evaluated in a phase I clinical trial (NCT04111458) as a single agent or in combination with trametinib (MEK inhibitor) in patients with KRAS mutated cancers. Results have not been published.

5.2.2 SHP2 inhibitors|—The protein SHP2 is a tyrosine phosphatase encoded by the gene *PTPN11* that is involved in signal transduction in various signaling pathways including KRAS MAPK signaling. Its role in KRAS signaling is still incompletely understood, but it is thought to recruit other critical proteins such as SOS1 and GRB2 [106–108]. Although SHP2 is a phosphatase, it has a positive activating role in KRAS signaling and is considered a critical protein in oncogenic signaling. SHP2 plays an important role in cancer development in KRAS-mutated PDAC and NSCLC models, and its deletion delays progression of established PDAC and NSCLC xenografts in mice [109]. Targeting SHP2 showed synergy with MEK inhibition and resulted in tumor growth inhibition in PDAC and NSCLC models *in vivo* [109]. Moreover, it was shown recently that SHP2 is essential for the remodeling of the vasculature in melanoma and colon cancer tumor models, and its inhibition impairs the tumor vasculature, thus reducing tumor growth [110]. Whether SHP2 plays a similar role in PDAC remains to be seen.

SHP2 has an intrinsic regulatory mechanism, as it is found in a closed conformation due to intramolecular domain-domain interactions that prevents access of its active site [111]. This autoinhibitory state was the basis for a screen to find a molecule that would lock SHP2 in its inactive autoinhibited state [112]. The compound SHP099 was discovered, and it was able to suppress MAPK signaling and reduce tumor growth *in vivo* [112]. This discovery catalyzed drug development efforts to target SHP2, which resulted in multiple clinical candidates that are in various stages of clinical testing [113]. RMC-4630 is currently in phase I/Ib clinical trials as monotherapy or in combination with an ERK inhibitor (NCT03634982, NCT04916236). RMC-4630 is based on the molecule RMC-4550 which was shown preclinically to inhibit proliferation of tumor cells harboring certain KRAS mutations [114]. Another SHP2 inhibitor, TNO155, is currently in several phase I and II clinical trials as a monotherapy or in combination with various targeted therapies (NCT04000529, NCT04330664, NCT03114319). TNO155 was discovered through structural and property-based design of a lead molecule discovered in a high throughput screening approach to find an allosteric inhibitor of SHP2. TNO155 was able to inhibit MAPK signaling and reduce tumor growth *in vivo* [115], and was found to be synergistic with several other drugs which are being tested in clinical trials [116]. Several other SHP2 inhibitors are also in clinical trials, including ERAS-601 (NCT04670679), JAB-3312 (NCT04121286), BBP-398 (NCT04528836), and RLY-1971 (NCT04252339). Little detail is available about these inhibitors, and results from the trials are not yet available.

5.2.3 Cancer vaccination—Cancer vaccination has recently emerged as a potential immunological therapeutic strategy. Tumors have neoantigens, and they can be utilized to vaccinate the patient to stimulate the immune system to attack cancer cells that present those antigens. This approach has been mostly studied as a personalized medicine approach, with each patient vaccinated with antigens specific to their tumor [117–120]. Recently, a new mRNA vaccine has entered a phase I clinical trial. mRNA-5671/V941 encodes mutant KRAS and is being investigated in patients with KRAS-mutant tumors (NCT03948763) (Fig. 2). In preclinical models, strong T-cell responses were elicited after vaccination in mice with two different (unspecified) KRAS mutations [110]. The clinical trial is testing the vaccine as a single agent or in combination with the monoclonal anti PD-1 antibody, pembrolizumab. Other types of vaccination for KRAS mutated patients are also in clinical trials, including dendritic cell vaccines (NCT03592888) and peptide vaccines (NCT04117087).

5.2.4 Adoptive cell therapies—Adoptive cell transfer is an immunotherapeutic approach where the patient's lymphocytes, which either have anti-tumor specificity or are manipulated to target tumor antigens, are expanded *ex vivo* and then infused back into the patient [121]. Identifying a safe and efficient antigenic target is critical when manipulating the specificity of the lymphocytes [122]. Tumor neoantigens are the most suitable target since they are virtually foreign antigens where central tolerance was not induced, thus increasing efficiency and minimizing toxicities [123]. RAS oncogene has long been known to be immunogenic. Recently, a patient with metastatic colorectal cancer was found to have KRAS G12D reactive T-cells within the tumor-infiltrating lymphocytes (TILs) [124]. The patient was treated with a transfer of an expanded population of TILs with 4 different specificities to mutant KRAS G12D, and all seven of the patient's metastatic lesions regressed [124]. This showed that adoptive transfer of T-cells with mutant KRAS specificity is a valid therapeutic approach that could potentially benefit patients with these mutations. Two clinical trials were started to investigate a therapeutic approach that uses the patient's peripheral lymphocytes which are transduced with murine T-cell receptors that target mutant KRAS G12D (NCT03745326) or G12V (NCT03190941). These therapies are HLA-restricted, which is required for the recognition of the tumor cells by the mutant KRAS specific T cells. Although these therapies were promising, the trials have since been suspended, and no results have been reported. It remains to be seen whether any other cell-based immunologic therapies would be developed and would benefit pancreatic cancer patients.

5.3 Emerging strategies in preclinical development

5.3.1 PROTAC—Proteolysis targeting chimeras (PROTACs) are an emerging therapeutic approach to target proteins of interest for degradation, and it is an especially attractive area of research for protein targets that are considered undruggable using small molecule inhibitors (Fig. 2) [125]. PROTACs are composed of two peptides that are linked together: one is a ligand of the target protein, and the other recruits an E3 ubiquitin ligase to ubiquitinate the target protein and mark it for proteasomal degradation. A PROTAC called LC-2 that targets mutant KRAS G12C has been developed which is composed of MRTX849 linked to a VHL recruiter peptide [126]. MRTX849 binds covalently to mutant KRAS, and

then VHL E3 ligase is recruited and mutant KRAS is destroyed by ubiquitin-mediated proteasomal degradation [126]. LC-2 resulted in sustained degradation of KRAS and inhibition of MAPK signaling [126]. Another PROTAC was developed to target PDEδ, which is critical for KRAS diffusion in the cytosol and its plasma membrane localization [127]. The compound 17f was able to degrade PDEδ, diminish KRAS signaling, and inhibit cellular proliferation and tumor growth in a colorectal cancer model with mutated KRAS [128]. For implementation in the clinic, these compounds need further development to enhance the efficacy and potency. These preclinical studies represent proof of concept for a promising novel therapeutic approach for KRAS.

5.3.2 α4–α5 interface inhibitors—A monobody termed NS-1 has been developed as a biologic that targets the α4–α5 interface of KRAS [129–131]. This inhibitor prevents the dimerization of RAS, thus blocking RAF activation and downstream signaling [131]. Intracellular expression of NS-1 was able to prevent the formation and progression of pancreatic cancer in mice [132]. This shows that targeting this new site is a potential strategy for KRAS inhibition. However, cellular permeability of large molecules such as NS-1 is an obstacle, and thus further drug development is required to target the α4–α5 interface.

6. Novel combinations

KRAS signaling pathways are highly diverse and interconnected; therefore, abrogating KRAS signaling is not a trivial task. We highlight here some of the novel targeted therapy combinations that are in clinical and preclinical testing (Tables 2 and 3). Combinations have the advantage of potentially targeting multiple aspects of KRAS signaling at the same time, which could result in more efficacious attenuation of signal transduction. Recently, genomic studies have revealed co-occurring mutations in KRAS mutated PDAC which can be utilized to develop potential therapeutic combinations that target the genes and the pathways that are involved in PDAC [7, 133]. These pathways include MAPK and PI3K-AKT-mTOR pathways downstream of KRAS, as well as EGFR overexpression upstream of KRAS [134, 135]. Additionally, DNA damage repair genes have been implicated in PDAC tumorigenesis, as deficiencies in BRCA and mismatch repair genes (MMR) have been identified as major mutational mechanisms [7], and therefore represent targetable therapeutic vulnerabilities. Development of combinatorial targeting strategies is an important approach to combat resistance against single agent therapy. One approach is vertical combinations, where multiple proteins of the same pathway are targeted, for instance targeting multiple effectors of the KRAS-RAF-MEK-ERK signaling pathway. The other approach is horizontal targeting, where targets across different KRAS downstream pathways are inhibited at the same time.

Novel therapeutic vertical combinations include SHP2 inhibitor combinations with novel KRAS G12C inhibitors, with ERK inhibitors, or with MEK inhibitors. Combining SHP2 inhibitor with KRAS G12C inhibitors ARS-1620 and AMG 510 in a panel of pancreatic, colon, and lung cancer cell lines harboring G12C mutation resulted in sustained KRAS signaling attenuation and prevented feedback reactivation of RAS signaling compared to G12C single agent inhibition [136]. Similar combinations are being investigated clinically; a combination of MRTX849 with TNO155 (SHP2 inhibitor) is being evaluated for solid

tumors in a phase I/II clinical trial (NCT04330664), and another trial is being conducted to evaluate the combination of JDQ443, a KRAS G12C inhibitor, with TNO155 or spartalizumab, a PD-1 inhibitor (NCT04699188). These trials are currently recruiting, and results have not yet been reported.

Evidence suggests that SHP2 inhibition is a potential strategy to limit adaptive resistance to ERK pathway inhibition in KRAS mutant cancers [137, 138]. A new phase I/Ib clinical trial is going to study the combination of a SHP2 inhibitor, RMC-4630, with an ERK inhibitor, LY3214996, in patients with metastatic pancreatic, colorectal cancer, and NSCLC which harbor KRAS mutations (NCT04916236). Additionally, combinations of various SHP2 inhibitors with MEK inhibitors are being evaluated in clinical trials (NCT04670679, NCT03989115).

Additionally, KRAS G12C inhibitors are in combinatorial trials with various targeted and immunological therapies. Although checkpoint inhibitors have had great success in various cancers, most trials in PDAC did not show significant benefit [139]. Trials are investigating combinations of G12C inhibitors with checkpoint inhibitors for possible synergy (NCT04185883, NCT04613596) [61]. Synergy between G12C inhibitors and checkpoint inhibitors would provide proof of concept for future combinations with any novel G12D or G12V inhibitors, which would benefit a greater proportion of pancreatic cancer patients. Other investigational combinations with G12C inhibitors include MEK inhibitors, EGFR inhibitors, mTOR inhibitors, CDK 4/6 inhibitors, and VEGF inhibitors.

A dual RAF-MEK inhibitor, VS-6766/ CH5126766/ RO5126766, that targets the kinase activity of RAF and MEK simultaneously has been tested clinically in certain malignancies [140–142]. In preclinical evaluation, VS-6766 was able to suppress RAF and MEK kinase activity in a panel of cancer cell lines including KRAS mutated PDAC cells, was able to reduce tumor growth in NSCLC and colorectal carcinoma (CRC) mouse models, and showed synergy with G12C inhibitors in NSCLC and CRC cells [143–145]. The combination of VS-6766 with defactinib has been recently granted breakthrough therapy designation by the FDA, which came after encouraging results from the phase II FRAME trial (NCT04625270) for ovarian cancer irrespective of KRAS mutation status [146]. Nonetheless, KRAS mutant patients had a higher ORR (70%) than patient with wild-type KRAS (52%) [146]. A phase II clinical trial is underway to evaluate the combination in KRAS mutated solid tumors (NCT04620330).

Another combinatorial approach is targeting multiple arms of KRAS signaling. Co-targeting of the MAPK and PI3K pathways has been explored as a strategy to prevent adaptive resistance that results from the activation of one of those pathways upon the inhibition of the other. Clinical trials have investigated combinations targeting both MAPK and PI3K pathways, including combinations of PI3K and MEK inhibitors, AKT and MEK inhibitors, and mTOR and MEK inhibitors. Although these combinations showed synergistic activity in preclinical models, there were issues of tolerability and rate-limiting toxicities in clinical trials.

Finally, some combinations aim to target KRAS pathways in addition to cellular processes that are known to be deregulated in pancreatic cancer, such as autophagy. Autophagy is upregulated in PDAC cells [35] and is thought to be implicated in chemotherapy resistance [147]. Thus, autophagy has been investigated as a potential target for PDAC. Hydroxychloroquine is an anti-malaria medication that inhibits autophagy and has been studied in a phase II clinical trial as monotherapy for PDAC without much clinical benefit [148]. Combinations of chloroquine or hydroxychloroquine with gemcitabine have also been tested in clinical trials but failed to show any therapeutic benefit over gemcitabine alone [149, 150]. Interest remains in autophagy inhibition in combination with targeted therapeutics to treat KRAS mutant PDAC. Preclinical studies have shown that inhibition of autophagy was synergistic with MAPK pathway inhibitors in PDAC models. Combinations of MAPK pathway inhibition (ERK or MEK inhibitors) with hydroxychloroquine are currently being investigated in multiple clinical trials for malignancies with KRAS mutations (NCT04145297, NCT03825289, NCT04132505, and NCT04214418).

7. Mechanisms and strategies for overcoming resistance

Although novel inhibitors of mutant KRAS and its downstream targets showed promising results in preclinical and clinical investigations, studies to understand the mechanism of resistance to mutant KRAS or downstream pathway inhibitors are very limited. Recent investigations in a cohort of 38 NSCLC patients treated with KRAS G12C inhibitors revealed resistance development in 45% of the patients. Notable acquired genetic changes in KRAS were G12D/R/V/W, G13D, Q61H, R68S, H95D/Q/R, Y96C, and KRAS G12C allele amplification [151]. Such mutations may elevate the levels of GTP-bound active KRAS protein and can prevent binding to drugs [91]. Amplification of MET; mutational activation of NRAS, BRAF, MAP2K1, and RET; oncogene fusion including ALK, RET, BRAF, RAF1, and FGFR3; and loss-of-function mutations in NF1 and PTEN were also shown to play a significant role in the development of resistance [151]. It has been demonstrated that KRAS inhibition mediated by mutant KRAS inhibitors, including KRAS G12C inhibitor sotorasib, or MEK inhibitors, such as trametinib, leads to adaptive resistance in PDAC [152]. Such inhibition causes integrin-linked kinase (ILK) mediated activation of the mTORC2 molecule RICTOR and phosphorylation of AKT at Ser-473 in several PDAC mouse models and human tumors [152]. It is evident that RICTOR expression is correlated with poor prognosis in PDAC patients [153], and both RICTOR/mTORC2 activations are associated with PDAC progression [154]. Inhibition of mTORC2 alone stimulates phosphorylation of ERK [152, 155] resulting in increased cell survival. However, in combination with mutant KRAS or MEK inhibitor, it promotes cell death in PDAC cells [152], suggesting an important role of mTORC2 signaling in the resistance of PDAC.

In another study, Chen et al. observed that murine PDAC cells can tolerate acute and sustained KRAS silencing by activating a reversible cell state [156]. The study used an RNAi-based inducible system for conditional silencing of KRAS at both alleles. The reversible state was characterized by morphological changes, proliferative kinetics, and the capacity for tumor initiation. Although no mutational or transcriptional alterations were found during the KRAS-silenced state, global phosphoproteomic analysis revealed the involvement of a number of cellular signaling events including the activation of the

focal adhesion pathway. Such findings indicate that focal adhesion signaling is a possible resistance mechanism to KRAS inhibition. Identification and targeting of key molecules of this pathway may overcome resistance to KRAS inhibitors. Although targeting of focal adhesion kinase (FAK) or SRC was not sufficient to induce cell death in KRAS-inhibited cells selectively, other molecules of this pathway could be potentially targeted which warrants further investigation [156]. Moreover, alterations of multiple RTK-RAS-MAPK pathways also contribute to the resistance to the KRAS G12C inhibitor adagrasib resistance, and clinical trials combining RTK or SHP2 inhibitors with mutant KRAS inhibitors are underway (NCT04330664, NCT04185883) [151]. Additionally, alternative prenylation against FTI therapy as described above plays a role in the development of resistance. It is important to understand the mechanism of resistance against novel KRAS targeted inhibitors to ensure sustained and durable remissions. In-depth understanding of resistance mechanisms is crucial for optimal therapeutic targeting of PDAC even when mutation specific KRAS inhibitors are unavailable.

7.1 The role of tumor microenvironment in resistance

The TME of PDAC plays an important role in the development of resistance [157]. CAFs have been implicated in driving the desmoplastic response in PDAC [59, 158], which ultimately contributes to the resistance to various therapies [159] including KRAS targeting agents. A mechanistic study revealed that CAF's expressed vitamin D receptor is involved in the development of resistance, and calcipotriol, a vitamin D receptor agonist, can revert CAFs to their original state in a mouse model [160]. Such targeting of tumor stroma could potentially enhance the delivery of KRAS specific inhibitors or other targeting agents. Recently in 2020, Hou et al. observed an upregulation of HDAC5 in a gain-of-function study in the inducible KRASG12D/Trp53−/− PDAC mouse model [161]. The epigenetic regulation mediated by HDAC5 enhanced the recruitment of macrophages into the TME, which promotes resistance to KRAS targeting. An increase in CCL2, due to the suppression of its negative regulator SOCS3, helps in the recruitment of macrophages. These tumor-associated macrophages (TAMs) can support cancer cells by bypassing KRAS signaling through the activation of TGF-β in a SMAD-4 dependent manner [161]. Therapy resistance in PDAC could also result from autophagic degradation of CAFs which releases different metabolites that are utilized by the cancer cells [159, 162–164]. The secretion of metabolites with structural similarity to drugs by CAFs, such as the metabolite deoxycytidine which is similar to gemcitabine, enhances the tumor's capability of drug resistance [165, 166]. Besides CAFs, neurons present in the TME can support PDAC growth by releasing amino acid serine [162].

KRAS mutated TME includes numerous types of cells. Targeting cell types that significantly contribute to PDAC growth along with KRAS pathway targeting agents could potentially be a sustainable strategy to overcome resistance. Targeting autophagy of both tumor cells and CAFs is a promising approach to inhibit tumor growth in *in vivo* [167] and can be combined with KRAS targeted agents. Additionally, targeting TME recruited neurons in PDAC using TRK inhibitor [168] along with KRAS targeted inhibitors could be a novel approach. Research showed convincing findings of simultaneous targeting of TGF-β and oncogenic KRAS using antifibrotic fraxinellone-loaded CGKRK-modified nanoparticles

(Frax-NP- CGKRK) and siRNA-loaded lipid-coated calcium phosphate (LCP) biomimetic nanoparticles (siKras-LCP-ApoE3) respectively in a pancreatic cancer mouse model [169]. Additionally, combining a SHP2 inhibitor with KRAS G12C inhibitor successfully abrogated RTK feedback signaling and adaptive resistance to G12C inhibitor in *in vitro*, xenograft, and syngeneic KRAS G12C-mutant PDAC model [170]. This combination was shown to remodel the tumor immune microenvironment by decreasing myeloid suppressor cells and increasing CD8+ T cells [113, 170].

8. Conclusion

Despite decades of intensive research, pancreatic cancer remains a highly lethal malignancy with an extremely poor prognosis, and cytotoxic therapeutics provide minimal benefit for pancreatic cancer patients. The newly approved and emerging KRAS G12C inhibitors could only benefit a small subset of pancreatic cancer patients, whereas there are no approved drugs to target KRAS G12D and G12V, the major mutations in PDAC. Nonetheless, there is now renewed hope that KRAS could be a targetable oncogene, and several promising advances have been made in the field including direct and indirect targeting strategies. Combinations of various targeted therapeutics and immunotherapy seem to be the direction that holds most promise for the future for PDAC patients. Clinical trials are actively investigating the therapeutic targeting of multiple KRAS-related pathways and molecules. Results from these trials would inform future research directions and clinical trials on tailoring the correct combinations according to the molecular alterations for each patient's cancer, as well as elucidating the mechanisms of resistance to tackle it when it arises. In light of the successes of G12C inhibitors, ongoing work to develop other specific mutant KRAS inhibitors could potentially result in promising new therapeutic approaches to target the major driver mutations in PDAC. Finally, research into combining KRAS targeted drugs with pancreatic tumor microenvironment modulating agents for enhanced drug delivery and efficacy will be promising avenues of future therapeutic strategies.

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Conflict of interest

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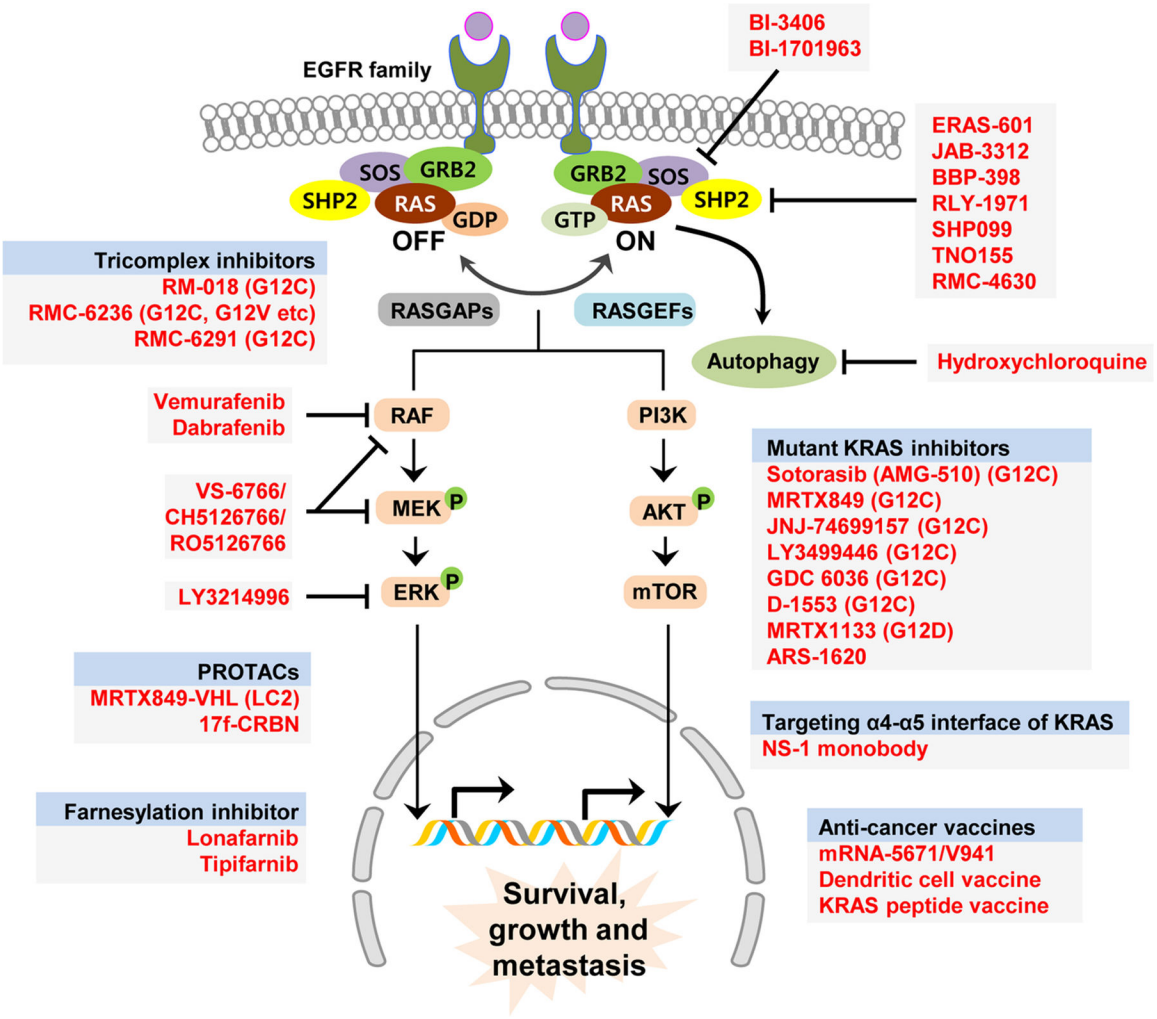

Fig. 1. Schematic illustration of KRAS pathway and targeted preclinical and clinical agents.

Receptors in the EGFR family upstream of KRAS transmit extracellular signals to activate KRAS. KRAS is activated via GDP to GTP exchange catalyzed by GEFs such as SOS, whereas GAPs catalyze the GTPase activity of KRAS. Downstream signaling pathways include the RAF/MEK/ERK and PI3K/AKT/mTOR pathways, which result in the expression of genes that promote survival, growth, and metastasis. Inhibitors or other targeted agents in the upstream or downstream of KRAS signaling have been depicted. RASGAPs RAS GTPase activating proteins, RASGEFs RAS guanine exchange factors, CRBN cereblon, PROTACs proteolysis targeting chimeras, VHL Von Hippel–Lindau tumor suppressor

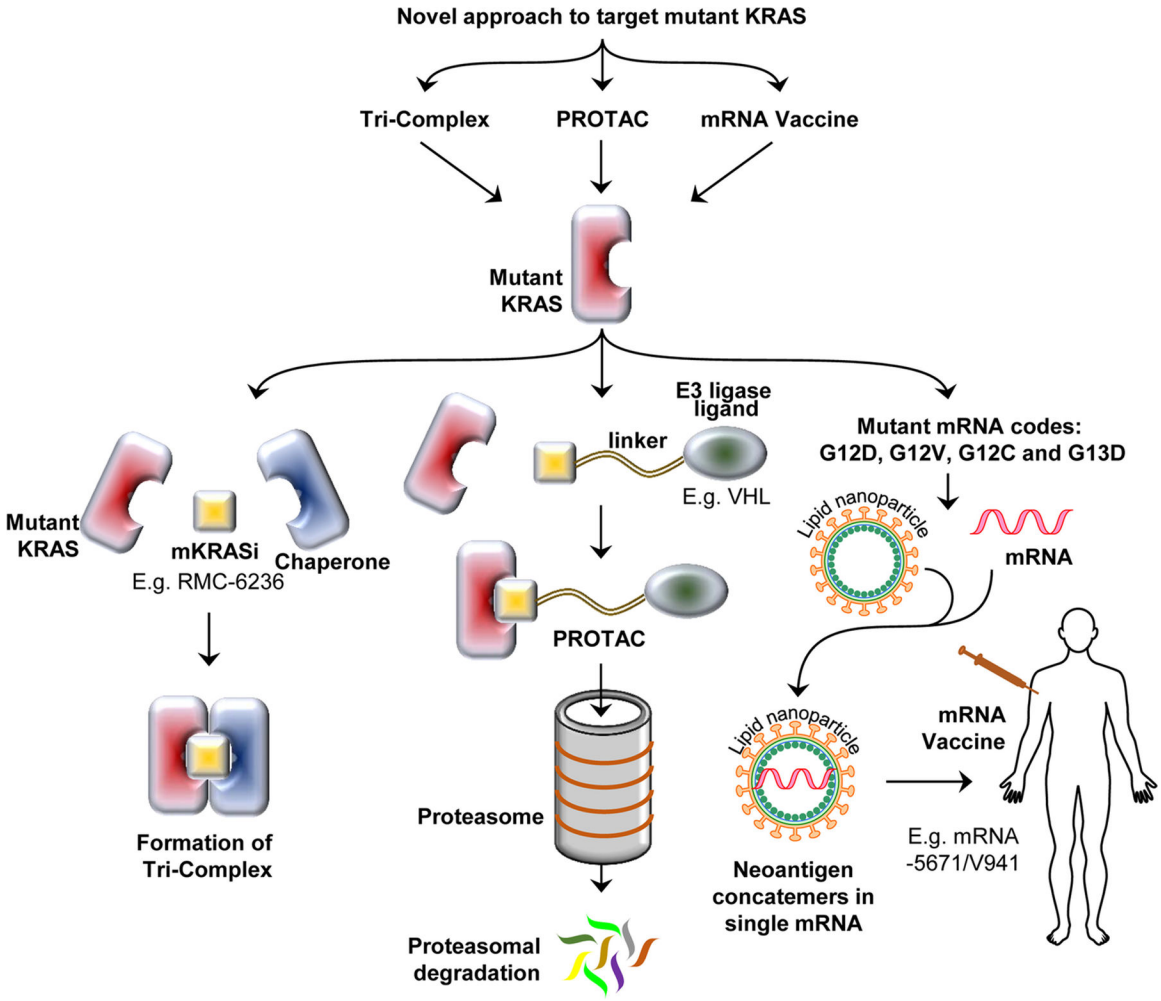

Fig. 2. Various novel approaches to target mutant KRAS.

Basic concepts of targeting mutated KRAS using tricomplex inhibitors, PROTACs, and mRNA vaccine have been illustrated in the figure. Tricomplex inhibitors utilize an endogenous chaperone protein to create a novel pocket for small molecule KRAS inhibitors. PROTACs recruit an endogenous E3 Ligase to mutant KRAS, thus targeting it for proteasomal-mediated degradation. mRNA vaccines utilize the mRNA code of mutant KRAS, encapsulated in a lipid nanoparticle to stimulate the immune response against tumor-associated neoantigens. mKRASi mutant KRAS inhibitor, PROTACs proteolysis targeting chimeras, VHL Von Hippel–Lindau tumor suppressor

Table 1

Unsuccessful studies in targeting KRAS in pancreatic cancer

Agent	Rationale	Mechanism of resistance	Reference
Farnesyl transferase inhibitors (FTIs)	Prevention of KRAS plasma membrane localization	Alternative prenylation by geranyl geranyl transferases, which allows KRAS localization at the plasma membrane	[68–70]
RAF inhibitors (e.g., vemurafenib)	Inhibition of KRAS mediated RAF activation and downstream signaling	RAF inhibitors bound to wild type RAF in KRAS mutant cells, resulted in the formation of RAF dimers that activated downstream signaling	[77–80]
mTOR inhibitors (e.g., everolimus)	Inhibition of PI3K pathway downstream of KRAS	Activation of alternative downstream pathways; Paradoxical AKT phosphorylation and cyclin D1 activation leading to increased proliferation.	[85, 86]

Table 2

Clinical development of strategies to target KRAS in cancer

Agent	Target	Clinical trial number (Clinicaltrials.gov)	Remarks
Sotorasib (AMG-510)	Direct mutant KRAS G12C covalent inhibitor	NCT03600883 NCT04185883 NCT04933695 NCT04303780	Sotorasib obtained accelerated FDA approval. Ongoing phase Ib, II, and III trials for patients with G12C mutations.
MRTX849	Direct mutant KRAS G12C covalent inhibitor	NCT04330664, NCT03785249 NCT04685135 NCT04793958 NCT04613596	KRYSTAL trials: Phase I/II trials for patients with G12C mutations. Phases II and III trials for NSCLC and CRC patients with G12C mutations.
LY3499446	Direct mutant KRAS G12C covalent inhibitor	NCT04165031	Trial terminated due to unanticipated toxicities.
JNJ-74699157	Direct mutant KRAS G12C inhibitor	NCT04006301	Trial completed, no results reported
GDC 6036	Direct mutant KRAS G12C inhibitor	NCT04449874	Phase I trial for tumors with G12C mutations.
D-1553	Direct mutant KRAS G12C inhibitor	NCT04585035	Phase I/II trial for tumors with G12C mutations.
BI-1701963	SOS1 inhibitor	NCT04111458	Phase I trial for solid KRAS mutated tumors.
RMC-4630	SHP2 inhibitor	NCT03634982 NCT04916236	Phase I/Ib trial for tumors with MAPK pathway hyperactivation, including KRAS mutated.
TNO155	SHP2 inhibitor	NCT04000529 NCT03114319 NCT04330664	Phase I and II trials
ERAS-601	SHP2 inhibitor	NCT04670679	FLAGSHP-1 phase I/Ib trial in advanced or metastatic solid tumors as a single agent or in combination with MEK inhibitor
JAB-3312	SHP2 inhibitor	NCT04045496 NCT04720976 NCT04121286	Phase I/IIa clinical trials for patients with solid tumors
BBP-398	SHP2 inhibitor	NCT04528836	Phase I trial for patients with advanced solid tumors
RLY-1971	SHP2 inhibitor	NCT04252339	Phase I trial for patients with advanced solid tumors. However, it excludes patients with KRAS G12D, G12V, G13X, and Q61X mutations.
mRNA-5671/V941	Mutant KRAS mRNA vaccine	NCT03948763	Phase I trial for KRAS mutated solid tumors
KRAS peptide vaccine	Mutant KRAS long peptide vaccine	NCT04117087	Phase I trial in CRC and PDAC
mDC3/8-KRAS Vaccine	Dendritic cell vaccine	NCT03592888	Phase I trial in KRAS mutated resectable PDAC
Anti-KRAS G12D/ G12V mTCR PBL	Adoptive cell transfer	NCT03745326 NCT03190941	Trials have been suspended.

CRC colorectal carcinoma, *FDA* food and drug administration, *mTCR PBL* murine T-cell receptor transduced peripheral blood lymphocytes, *PDAC* pancreatic ductal adenocarcinoma

Table 3

Preclinical development of novel strategies to target KRAS in pancreatic cancer

Agent	Target	Mechanism of action	Reference
Tricomplex inhibitors (RMC-6291, RMC-6236)	Direct mutant KRAS inhibitors	Small molecule binds a chaperone protein forming a complex that binds to KRAS in a tricomplex that prevents KRAS-mediated signaling.	[98]
KD2 cyclic peptide	Direct mutant KRAS inhibitor	Binds and inhibits the GTP-bound form of mutant KRAS G12D in the switch II groove	[97]
KS-58 bicyclic peptide	Direct mutant KRAS inhibitor	Cyclic peptide with unnatural amino acids that binds mutant KRAS G12D	[99]
MRTX1133	Direct mutant KRAS inhibitor	Binds mutant KRAS G12D	[100]
NS-1	α4–α5 interface inhibitor	Monobody that binds KRAS surface preventing dimerization.	[129, 130, 132]
LC-2	PROTAC targeting mutant KRAS	PROTAC composed of MRTX849 linked to a VHL recruiter, resulting in ubiquitin-mediated proteasomal degradation of KRAS G12C	[126]
17f	PROTAC targeting PDEδ	Degradation of PDEδ prevents KRAS localization at plasma membrane, thereby preventing signaling.	[128]