# **Therapeutic Targeting of KRAS Oncogene in Pancreatic Ductal Adenocarcinoma (PDAC)**

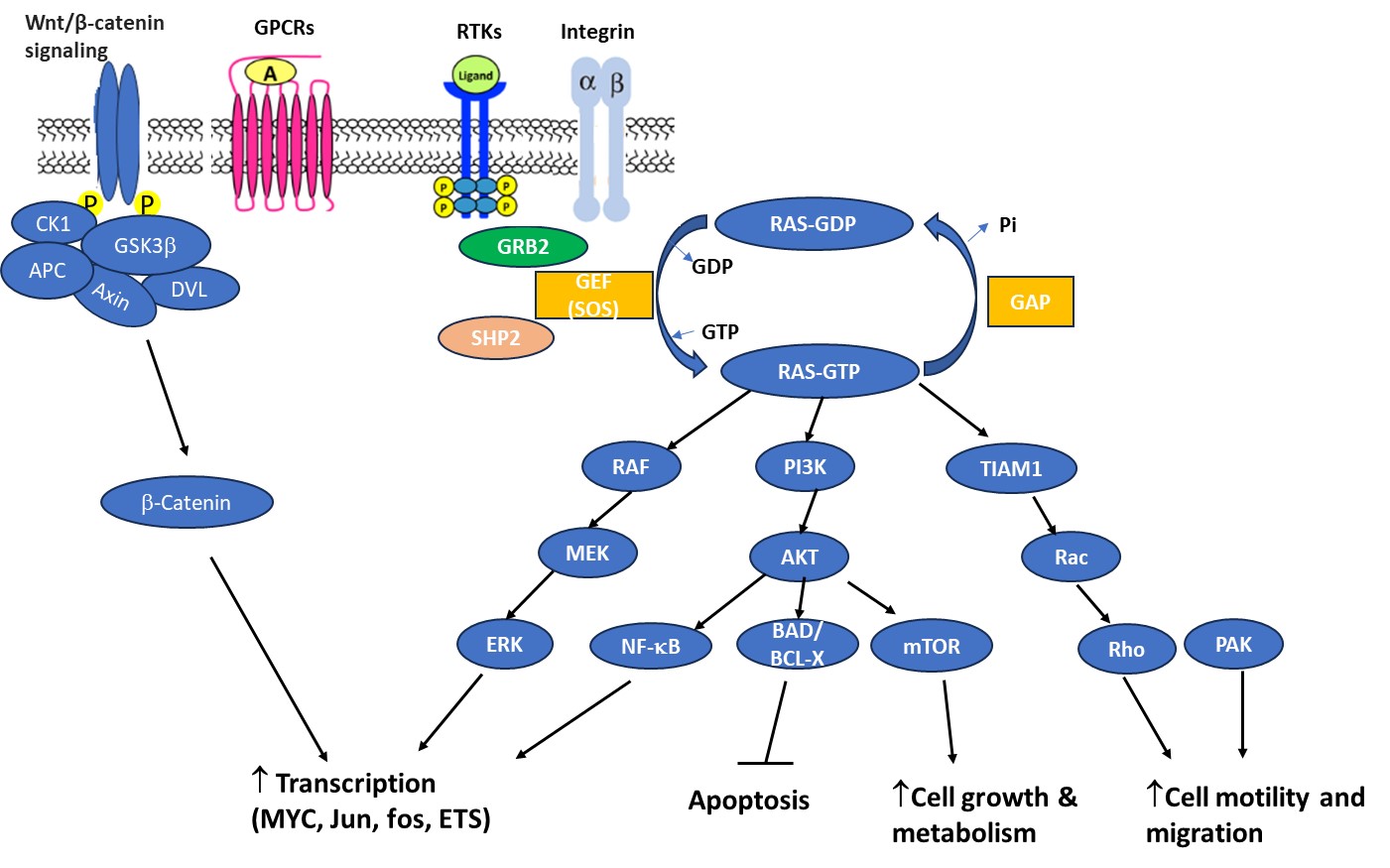
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**Introduction**

Pancreatic cancer is one of the most lethal forms of cancer, with a 5-year survival rate of only 9% (Ryan et al., 2014). In 2023, approximately 64,050 patients will be diagnosed with pancreatic cancer in the USA, and approximately 50,550 will succumb to the disease (Siegel et al., 2023). Around 85% of pancreatic cancers are Pancreatic ductal adenocarcinoma (PDAC). The onset of PDAC is closely related to mutations in four proteins, with their prevalence in PDAC patients indicated below: KRAS (~85%), Tumor protein 53 (TP53, 60–70%), cyclin-dependent kinase inhibitor 2A (CDKN2A, >50%), and suppressor of mothers against decapentaplegic homolog 4 (SMAD4, ~50%) (Luo, 2021). Genetic analysis of clinical specimens indicates that KRAS mutation is an early event present in stage 1 pancreatic intraepithelial neoplasia (PanIN). Acquisition of mutations in CDKN2A, TP53, and SMAD4 are associated with PanIN progression and the development of invasive PDAC**.** The high prevalence of KRAS mutation in PDAC suggests that the RAS signaling pathway is a key oncogenic driver of PDAC development. KRAS, therefore, is a prime target for PDAC treatment. In this review, the recent advancements in understanding the molecular basis of PDAC, treatment strategies, as well as clinical trials in progress are thoroughly evaluated through a review of the literature and a comparison of clinical trial outcomes.

The RAS family of GTPases is encoded by three ubiquitously expressed genes, HRAS, KRAS, and NRAS, that share significant sequence homology. The GTPase cycles between GTP-loaded ‘on’ (active) and GDP-loaded ‘off’ (inactive) states via reactions catalyzed by RAS-guanine exchange factor (RAS-GEF) and RAS-GTPase activating enzymes (RAS-GAPs) (Gimple & Wang, 2019), as illustrated in **Figure 1**. The RAS-GEF converts RAS from an inactive GDP-bound state to an active GTP-bound state, while the RAS-GTPase reverts the activated RAS to the GDP-bound, inactive state (Bos et al., 2007). The KRAS molecules are activated by cellular receptors, including receptor tyrosine kinases (RTK), G-protein coupled receptors (GPCRs), and integrin family members (Gimple & Wang, 2019). The activated cellular receptors recruit the molecular scaffolding protein Growth Factor Receptor Bound Protein 2 (GRB2), which in turn recruits the RAS-GEF SOS1 and converts RAS to the active form. SHP2, a cytosolic protein-tyrosine phosphatase, activates the SOS1-regulated RAS-GTP loading (Nichols et al., 2018).

Following activation, RAS can lead to a series of downstream cellular effects that promote cancer development including oncogenic transcription, cell cycle progression, cellular survival, cell growth and metabolism, and cell motility and migration (Gimple & Wang, 2019**)**. First, RAS activates the mitogen-activated protein kinase (MAPK) pathway defined by a RAF-MEK-ERK signaling axis (**Figure 1**). This pathway activates transcription factors (FOS, JUN, ETS, MYC) that support cell proliferation and survival. Second, RAS signals through the PI3K-AKT pathway, which activates transcription factor NF-κB, inhibits the pro-apoptotic enzyme BAD, and promotes cell growth and metabolism through mTOR. Third, activation of the TIAM1-Rac pathway drives cell motility and migration (**Figure 1**). KRAS can also promote transcription by synergistic actions with the Wnt-Catenin signaling pathway (Jeong et al., 2018). In normal cells, RAS receives signals and obeys those signals to rapidly switch between the active (GTP) form and the inactive (GDP form) states. RAS signaling in normal cells plays a critical role in cell growth, proliferation, and metabolism. However, in cancer cells, the mutated RAS remains activated (GTP-bound), leading to uncontrolled cell proliferation.

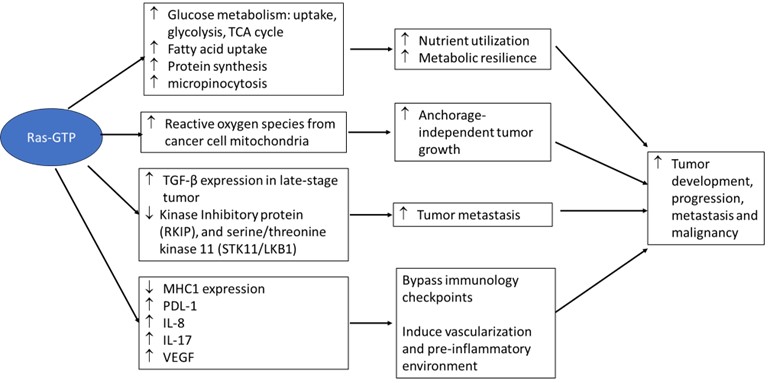


**Figure 1:** The RAS signaling pathway. Adapted from Gimple & Wang, 2019. Activation of the Ras signaling cascade and downstream efforts lead to increased transcription, cell growth, metabolism, motility, and migration. GPCR: G protein-coupled receptors, RTK: receptor tyrosine kinase

The RAS signaling cascade is highly regulated by post-translational modifications. Modifications including the conjugation of a farnesyl group (farnesylation), a fatty acid such as palmitic acid (palmitoylation), a single ubiquitin molecule (mono-ubiquitination), and dimerization promote membrane localization, activation, and efficient downstream signaling of the RAS molecule (Swarthout et al., 2005, Ambrogio et al., 2018). On the other hand, modifications including di-ubiquitination, where two ubiquitin monomers are covalently linked through an isopeptide bond, and acetylation, where an acetyl group is attached, have been shown to reduce RAS signaling activity (Yang et al., 2013).

**The Role of RAS In PDAC Cancer Development, Progression and Metastasis**

In PDAC patients, the activated RAS not only provides the genetic basis for tumorigenesis but also plays a critical role in tumor progression, and metastasis. RAS signaling pathway also modulates the interaction of cancer cells with the surrounding immunology microenvironment, which further sustains tumor growth and progression. The role of RAS in PDAC development, progression, and metastasis is elaborated below and summarized in **Figure 2**.



**Figure 2: The role of the RAS signaling pathway in cancer development, progression, and metastasis is elaborated.** Adapted from Gimple & Wang, 2019**.** The activated RAS promotes anchorage-independent cell growth through enhanced nutrient utilization and the production of reactive oxygen species from cancer cells; the activated RAS increases tumor metastasis by increasing the expression of TGF-β and reducing the expression of kinase inhibitor protein and serine/threonine kinase 11. The activated RAS modulates the surrounding immune micro-environment of cancer cells, making them less vulnerable to immunosuppression. The pre-inflammatory microenvironment, induced by the increased expression of IL-7, IL-8, and VEGF, further promotes tumor development and progression**.**

RAS in PDAC Tumorigenesis

The Cancer Genome Atlas (TCGA) project identified the receptor tyrosine kinase (RTK) -RAS signaling pathway as the most frequently altered oncogenic network in cancer (Sanchez-Vega et al., 2018). RAS mutations contribute to 20–30% of all human cancers. KRAS mutations are exceedingly common in pancreatic adenocarcinomas and colorectal cancers, with about 90% and 37% of patients bearing these mutations, respectively (Waddell et al., 2015; Markowitz and Bertagnolli 2009).

For PDAC patients, over 90% of the KRAS mutations result in amino acid substitutions at codon 12 (Cerami et al., 2012). The three common amino acid substitutions, G12D, G12R, and G12V are found in 41%, 16%, and 34% of the PDAC patients, respectively (Waters and Der, 2017). Codons 13 and 61 are also highly susceptible to amino acid substitutions. Mutations in these conserved sites favor GTP binding, creating a continuous active form of RAS. There is a strong correlation between mutant codons and the tissue impacted. For example, mutations in codon 12 are particularly associated with cancer in the gastrointestinal tract. Understanding the prevalence of RAS mutations in different cancer types provides an important opportunity for personalized treatment for patients.

RAS in the Progression of PDAC

As described earlier, mutations that activate RAS will lead to uncontrolled cell proliferation, enhanced survival, and migration for cancer cells. RAS mutations also support PDAC progression through enhanced metabolic resiliency. Specifically, RAS signaling enhances glucose uptake, promoting cancer cell survival in low-nutrient conditions. Mutant Ras enhances glycolysis and protein synthesis and directs metabolites into the tricarboxylic acid (TCA) cycle. All of these biochemical reactions enhance nutrient utilization and, therefore, promote tumor progression (Kerr et al, 2016). Reactive oxygen species generated from PDAC cancer cell mitochondria promote anchorage-independent cancer cell growth through modulation of the ERK signaling pathway (Weinberg et al., 2010). RAS-driven cancers can utilize nutrients from the extracellular environment through micropinocytosis (Bar-Sagi et al., 1986). This process further supports the growth of cancer cells while depleting nutrients for surrounding normal cells. In PDAC cancer cells, the enhanced mitochondria recycling and oxidative capacity are maintained through autophagy. Through autophagy, mitochondria and their components are captured, degraded, and recycled to maintain the increased mitochondria activity in cancer cells (Guo et al., 2016).

RAS in the Metastasis of PDAC

In PDAC patients, RAS activity is important for acquiring more malignant features, including metastasis. The metastatic phenotype was achieved by augmented transforming growth factor beta (TGF-β) signaling (Boutin et al., 2017), as well as repression of Raf Kinase Inhibitory Protein (RKIP) (Yang et al., 2018) and serine/threonine kinase 11 (LKB1) (Ji et al., 2007). In KRAS-driven pancreatic cancer models, deletion of LKB1 enhances the biosynthesis of S-adenosyl-methionine (SAM) and DNA methylation, enhancing PDAC metastasis (Kottakis 2016).

RAS In Modulating the Immunology Microenvironment of PDAC Cancer Cells

The cancer cells frequently gain proliferative advantage from the surrounding immunology microenvironment. Cancer cells exhibit aggressive and metastatic phenotypes by avoiding being targeted by the immune system. In RAS-driven pancreatic cancer, this is achieved by the following mechanisms: 1) reduced expression of MHC class I molecules on the surface of PDAC cells, rendering them less vulnerable to immune-mediated cell death by cytotoxic T-cells (Lohmann et al., 1996). 2) suppressed expression of PD-1 on immune cells and PD-L1 on PDAC cells (Loi et al., 2016). When suppressed, the PD-1/PD-L1 protein loses its activity to suppress immune-mediated PDAC cancer cell destruction (Coelho et al., 2017). Cancer patients with KRAS mutations have been shown to respond to PD-1 inhibitors (Borghaei et al., 2015). 3) the development of a pre-inflammatory microenvironment through the increased secretion of IL-8 and IL-17 (McAllister et al., 2014; Sparmann et al., 2004). Tumor vascularization, driven by RAS-mediated induction of hypoxic HIF signaling, and enhanced expression of vascular endothelial growth factor (VEGF) (Rak et al., 1995), contributes to the development of the pre-inflammatory microenvironment, as well as PDAC growth, progression, and metastasis.

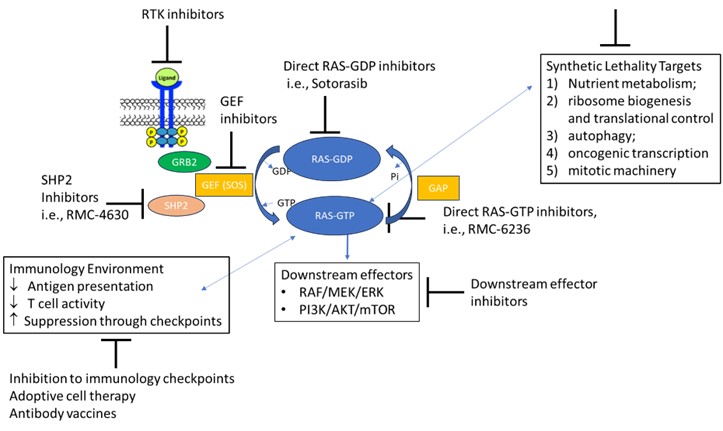
**Screening KRAS Mutations for Early PDAC Diagnosis**

The survival of PDAC patients remains poor due to the fact that the disease has often advanced significantly when diagnosed. Mutations in the KRAS oncogene are present in over 90% of resected PDAC specimens. The progression of PDAC from benign precursor lesions (PanIN) to invasive malignancy and metastases takes about 10-15 years. KRAS mutation is one of the earliest genetic events in PDAC evolution, present in PanIN lesions (Raphael et al., 2017). Identification of KRAS mutation in at-risk individuals could therefore serve as a useful screening tool for the detection of pre-invasive lesions prior to appearance using conventional imaging modalities. However, the detection of mutant KRAS-bearing circulating free DNA (cfDNA) has a sensitivity of only 20–25% when used to diagnose PDAC (Earl et al., 2015). This may be because a PDAC needs to be relatively advanced before sufficient mutant DNA is released into circulation. Sampling of pancreatic exocrine secretions has been shown to provide a higher sensitivity than the blood (Patel et al., 2020). Because PDAC originates from the ductal epithelium, it is expected that mutant KRAS is present in pancreatic secretions earlier than in the blood. The specificity of KRAS mutant cfDNA detection in pancreatic exocrine secretions may also be higher than in blood, as mutation detected in the blood may develop from cancers at sites other than the pancreas. A meta-analysis of 22 studies and a total of 2156 pancreatic cancer patients, revealed that the sensitivity of KRAS mutation testing in endoscopically sampled pancreatic mucus varies considerably and is not currently ready to be used as a diagnostic biomarker (Patel et al., 2020). However, it is useful as a screening tool to identify RAS-bearing individuals for prospective cohort studies.

**Therapeutic Options for PDAC**

For a long time after its discovery in 1982, RAS has not been considered a suitable target for direct inhibition due to three key biochemical features: first, the picomolar affinity of RAS proteins for GTP; second, the high intracellular concentrations of GTP (~500nM); and third, the absence of a deep or pharmacologically actionable small-molecule-binding pocket in the RAS proteins (Punekar et al., 2022). Due to the first two features, a small molecule medicine must possess unprecedented binding properties to overcome the picomolar affinity of RAS for GTP. Moreover, the GTP-binding site of the KRAS protein varies between specific KRAS mutants, such as the G12C, G12D, G12V, G13D, and Q61H variants (Lu et al., 2015), which further complicates KRAS inhibitor design.

In the past 10 years, a significant breakthrough has been in targeting RAS mutations and their effectors for PDAC treatment. Potential therapeutic targets for RAS mutant tumors are elaborated in this paper based on the mode of action (MOA) and summarized in **Figure 3**.



**Figure 3:** Therapeutic targets for RAS mutant tumors based on mode of action.

Direct RAS-GDP Inhibitors

Due to the difficulty of directly inhibiting GTP-bound mutant RAS as described above, first-generation direct KRAS inhibitors all bind to inactive, GDP-bound mutant KRAS (KRAS-off inhibitors). Towards this end, a major breakthrough was brought forward by the laboratory of K. Shokat in 2013. Compounds that bind covalently and selectively to KRASG12C-GDP were identified (**Ostrem et al., 2013**). X-ray crystallography revealed that the compounds form a stable covalent bond with the reactive mutant cysteine residue at codon 12 near Switch 2. This covalent bond prevents the RAS from switching from the “off-state” (GDP-bound) to the “on-state” (GTP-bound). Since the inhibition is specific to the G12C mutation in KRAS, the RAS signaling in non-malignant cells should not be affected. The risk of on-target, off-tumor toxicity is low. Two small molecule medicines using this mode of action, Sotorasib and Adagrasib are both in clinical trials. Response to both medicines has been demonstrated in PDAC patients who have developed tumor metastasis after original chemotherapy (Strickler et al., 2023; Bekaii‐Saab et al, 2022).

However, developing allele-specific inhibitors to more common RAS mutations in PDAC, i.e., G12D, G12V, and G12R, has been challenging due to the lack of a reactive residue that can form a covalent bond with a small molecule medicine. In 2022, an allele-specific G12D non-covalent inhibitor (MRTX1133) that inhibits the activity of RAS-G12D was discovered (Wang et al., 2022). MRTX1133 binding stabilizes the binding site by increasing the hydrophobicity, which induces the correlated movements of switches I and II. The movements then disrupt the interaction of RAS with its effector and regulatory proteins (Issahaku et al., 2022). MRTX1133 exerts potent, specific, and rapid antitumor activity against PDAC mouse models bearing KRASG12D mutations (Kemp et al., 2022). It has been demonstrated that MRTX133 not only inhibits the growth of PDAC cancer but also modulates the tumor microenvironment by enhancing the activity of macrophages and promoting the growth of micro-fibroblasts, which has been shown to restrain the growth of PDAC (Rhim et al., 2014)

Direct RAS-GTP Inhibitors

The RAS-GDP inhibitors (“off” inhibitors) are more susceptible to emerging resistance because of the upstream pressure that may promote new, second-site RAS mutations, or overexpression of receptor tyrosine kinase (Moore et al., 2020). Targeting the GTP-bound (“on” state) RAS can overcome these resistance mechanisms. Recently, several small molecules that target the “on-state” RAS have entered clinical trials. One such agent is RMC-6236 (Koltun et al., 2022). RMC-6236 non-covalently binds to an abundant intracellular chaperone protein, cyclophilin A (CypA), resulting in a binary complex that engages RAS “on” to form a high-affinity, RAS-selective, tri-complex that inhibits RAS binding to effectors (Koltun et al., 2022). Since RMC-6236 does not rely on the mutant cysteine binding around switch 2, it has been shown in preclinical models to have anti-tumor activity in multiple KRAS G12 isoforms including G12D, G12V, and G12R. Making it a very promising candidate for PDAC treatment.

Inhibition of RAS Activity Modulators

RAS modulators regulate the activity of RAS by three mechanisms: 1) regulate the localization of RAS to the plasma membrane, which then activates RAS for downstream signaling; 2) modulators that convert RAS from inactive (GDP-bond) to active (GTP-bound) form; and 3) modulate the activity of downstream effectors.

As described previously, RAS relies on post-translational modifications for localization to the cell membrane, activation, and effective downstream signaling. In preclinical models, Tipifarnib, a farnesylation inhibitor, demonstrated antiproliferative effects against pancreatic cancer cell lines at clinically relevant concentrations and displayed marked growth inhibition in pancreatic cancer models (End et al., 2001).

RAS-specific GEF SOS is an important therapeutic target because it converts RAS from inactive to active state. Small molecules that interrupt the RAS-SOS interaction have been shown to reduce downstream effector activation (Burns et al., 2014). The inhibition of the RAS binding domain, where activated RAS interacts with downstream effectors, impairs the interaction of RAS with RAF, Ral, and PI3K and reduces tumor growth in vitro and in vivo (Athuluri-Divakar et al., 2016). The kinase suppressor of RAS (KSR) serves as a scaffolding factor that links RAS to RAF and allows for MEK activation. Shielding KSR with a small molecule compound reduced oncogenic transcription (Dhawan et al., 2016). Protein tyrosine phosphatase SHP2 binds to receptor tyrosine kinase growth factor receptors through its SH2 domain and mediates activation of RAS through dephosphorylation, increasing its association with RAF. The SHP2 inhibitor has been shown to decrease cancer cell proliferation (Chen et al., 2016).

Downstream effectors in the RAS signaling pathway are important therapeutic targets for PDAC. More than 20 RAF/MEK/ERK and more than 40 PI3K/AKT inhibitors are currently in clinical trials (www.clinicaltrials.gov). Inhibition of the PI3K and MEK signaling pathways in PDAC patients bearing KRAS-G12D mutations has resulted in effective inhibition of tumor growth (Eser et al., 2013; Collisson et al., 2012).

Synthetic Lethality

Synthetic lethality means a protein, when suppressed or inhibited, results in cell death in the presence of activated oncogene (Kaelin, 2005). Synthetic lethality targets are essential for the survival of the cancer cells and therefore, provide important therapeutic targets. Several large-scale screens have been carried out using RNA interference-mediated expression silencing (Kim et al., 2016; Kumar et al., 2012) or the genome-wide forward genetic CRISPR screen tools to identify genes that are uniquely essential to the survival and proliferation of PDAC cancer cells (Castells-Roca et al., 2021). As revealed by the studies, the following intracellular pathways/ activities are augmented in RAS-bearing PDAC cancer cells and are potential therapeutic targets: 1) glucose/ lipid/ amino acid metabolism; 2) ribosome biogenesis and translational control; 3) autophagy; 4) increased oncogene transcription through NF-κB; 5) mitotic machinery and sensitivity to mitotic stress. Gemcitabine, a DNA synthesis inhibitor, and Olaparib, an inhibitor to poly ADP ribose polymerase (PARP), are both being investigated in PDAC clinical trials as targets that demonstrate synthetic lethality with cancer mutations (Wei et al., 2020, Qian et al., 2020).

Immunotherapy

Immunotherapy for RAS-mediated cancer has focused on the following aspects: 1) inhibition of negative regulators to the immune reactions (checkpoints, i.e., program death-1 or PD-1); 2) Chimeric antigen receptor (CAR) T cell therapy; 3) cancer vaccines.

The PD-1 immune checkpoint inhibitor pembrolizumab is the only immunotherapy that is FDA-approved for treating patients with advanced PDAC. In May 2017, pembrolizumab was approved for patients with unresectable or metastatic PDAC with progression on prior treatment with no satisfactory alternative treatment options. The FDA approval is based on the combined results of five multi-cohort, single-arm clinical trials evaluating pembrolizumab in patients with metastatic or unresectable solid tumors who had received a median of two prior lines of therapy. In one of the clinical trials (Le et al. 2017), the objective response rate (ORR) among the eight PDAC patients was 62% (2 patients had complete responses, 3 patients had partial responses, 1 patient had stable disease, and 2 patients were not evaluable).

In CAR T cell therapy, T cells are collected from the peripheral blood of patients with PDAC via leukapheresis and engineered to express chimeric antigen receptors directed toward a specific tumor antigen. These cells are subsequently expanded before reinfusion into patients (Srivastava and Riddell, 2018). Clinical trials for CAR T cells directed toward several tumor antigens including CEACAM5, mesothelin, HER2 neu, PSCA, and MUC-1 are currently in progress (Akce, et al., 2018).

A third immunotherapeutic approach to treat RAS-mutant tumors uses vaccines developed for RAS-mutant tumor antigens. One such approach involves the intradermal injection of peptides from mutant RAS proteins in combination with granulocyte–macrophage colony-stimulating factor (GM–CSF) (Klemp et al., 2001). In a phase I/II clinical trial, 32 PDAC patients were treated with a mutant-RAS-specific vaccine, Targovax TG-01, and gemcitabine (an inhibitor of DNA replication). Ninety-five percent of patients had a positive immune response. Median overall survival (OS) of 34.3 months, and median disease-free survival (DFS) of 19.5 months. (Palmer et al., 2020). Another approach utilizes the mRNA vaccine for mutant RAS. Results from Phase I clinical trials demonstrated that a personalized mRNA neoantigen vaccine can stimulate an immune response in patients with pancreatic ductal adenocarcinoma (PDAC). The vaccine, adjuvant autogene cerumen, was given after surgery. The vaccine was “highly immunogenic” in half of patients and may have delayed recurrence, said study presenter Vinod P. Balachandran, MD, of Memorial Sloan Kettering Cancer Center in New York, New York (Balachandran 2023).

Combination Therapy

As elucidated above, due to the complexity of the RAS signaling cascade, many drug have been developed to target the mutant RAS or other components in the RAS signaling pathway. The development of drug resistance and compensatory cancer signaling pathways suggests that combination therapy will provide additional benefits in the prevention of RAS-mediated oncogenesis.

An example is MRTX1133 in the treatment of PDAC patients bearing G12D mutations, the most prevalent RAS mutation in PDAC patients (Wang et al., 2022). MRTX1133 not only directly impacts cancer cell growth, including inhibiting cancer cell proliferation and modulating cancer cell apoptosis, but also shifts the tumor microenvironment (TME) (Kemp et al., 2022). T cells were necessary for MRTX1133's full anti-tumor effect, and T-cell depletion accelerated tumor regrowth after therapy. These results revealed that a combination of immunotherapy and anti-tumor therapy will likely provide better treatment for PDAC.

**Conclusions and Prospects**

PDAC is known for its high mortality rate and short survival period. Although some progress has been made in recent years regarding early diagnosis, perioperative management, and systemic treatment, the prognosis of patients has not improved significantly. Since KRAS is one of the most frequently occurring oncogenic mutations in PDAC, future candidates for PDAC therapies are likely to be achieved through targeting mutant RAS or other components of its signaling pathway.

For a long time, the treatment of KRAS mutations has been indirect, focusing on activity modulators, synthetic lethality, and immunotherapy. A breakthrough in the direct mutant RAS targeting was brought forward by the characterization of the binding pocket. The first generation of direct RAS-GDP is designed towards the G12C mutation. However, the direct inhibition of the more common KRAS mutations in PDAC, including G12D and G12V, has historically been challenging due to the lack of amino acids that can form a covalent bond with a small molecule medicine. Recently, MRTX1133, a small molecule that forms a non-covalent bond with mutant RAS has demonstrated efficacy towards the G12D mutation-mediated cancer including PDAC (Wang et al., 2022). The newer generation of RAS inhibitors target RAS in its GTP-bound, active state. RMC-6236, developed by Revolution Medicines Inc, is a first-in-class non-covalent RASMULTI(ON) inhibitor that is selective for the active, GTP-bound RAS. RMC-6236 has demonstrated deep and sustained regressions across multiple tumor types, particularly PDAC and NSCLC, harboring KRASG12X mutations (KRASG12X defined as mutation at codon 12 which encodes glycine (G) to X where X = A, D, R, S, or V). The Phase 1 clinical trial of RMC-6236 is currently ongoing with demonstrated encouraging anti-tumor activity in patients with previously treated NSCLC and PDAC (Arbour et al., 2023).

RAS does not only trigger carcinogenesis through interacting with multiple downstream effectors, but it also changes the tumor microenvironment through synthetic lethality with other intracellular activities or evades the control of the immune system by augmenting the immune checkpoints. Recent advancements in understanding of the role of RAS in PDAC tumorigenesis, progression, and metastasis suggest that a combination therapy that targets several different aspects of RAS-mediated cancer may be the most effective treatment for PDAC.

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