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A Review Article On Targeting The Kras In Cancer Therapy

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Abstract: KRAS is the most frequently mutated oncogene in lung carcinomas, accounting for 25% of total incidence, with half of them being KRASG12C mutations. RAS is one of the most well-known protooncogenes. It mutations occur in approximately 30% of all human cancers.

The KRAS gene can simultaneously harbor multiple mutations that can potentiate tumorpromoting activity. Therapeutic strategies tailored for KRAS+ NSCLC rely on the blockage of KRAS functional output, cellular dependencies, metabolic features, KRAS membrane associations, direct targeting of KRAS and immunotherapy. A comprehensive analysis of the different pathways and mechanisms associated with KRAS activity in tumors will ultimately pave the way for promising future work that will identify optimum therapeutic strategies. Over the years, a large number of studies have identified strategies at different regulatory levels to tackle this 'difficult-to-target' on co protein.

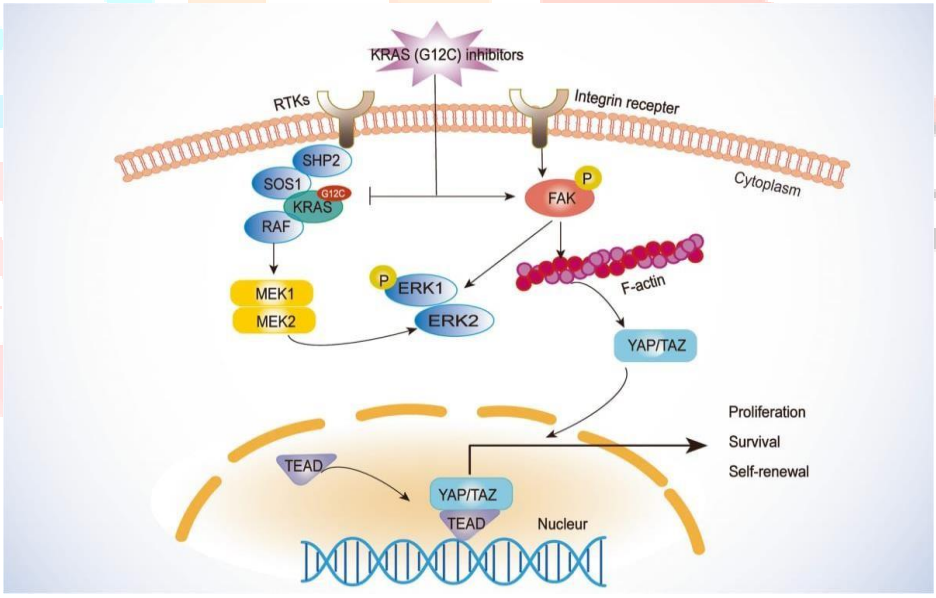
Keywords: Cancer; EGFR, KRAS, mutations, targeted-therapy

Introduction:

Mutations in Kirsten rat sarcoma viral oncogene homolog (KRAS) are one of the most common oncogenic events in endodermal carcinomas. Not only do KRAS mutations promote and maintain tumorigenesis, they also increase the chance of resistance and poor prognosis, ultimately contributing to over one million deaths annually. Among this growing list of oncogenes, KRAS, together with other RAS isoforms, represents the most prevalent oncogene in human cancers, yet decades long efforts in the discovery of RAS targeted therapies failed to obtain clinically approved drugs. Of note, recent years have witnessed the promising progress in exploring the therapeutic opportunities in RAS inhibition. As a wealth of excellent reviews has summarized the role of RAS signaling in driving tumorigenesis and possible direction of RAStargeted anticancer therapies. Scientists have been aiming to target KRAS for decades but have experienced difficulty in identifying strategies to target the smooth surface of the protein. Activating mutations in KRAS increase the ability for GTP-loading and the GTP binding pocket holds onto its substrate very tightly, making it difficult to displace. Thus, constitutive activation of downstream signaling of the mitogen-activated protein kinase (MAPK) pathway occurs and regulates proteins involved in cell proliferation, development, inflammation, differentiation and apoptosis to promote cancer formation. As a result, indirect strategies targeting downstream signaling of KRAS were attractive options but have still not resulted in desired outcomes. The epidermal growth factor receptor (EGFR) upstream of KRAS is also frequently mutated in various cancers and has also been sought as a therapeutic strategy to tackle KRAS mutant cancers. Despite the seemingly many options to target KRAS, there have been many failed attempts in the past.

KRAS (Kirsten rat sarcoma virus) is a gene that provides instructions for making a protein called K-Ras, a part of the RAS/MAPK pathway. The protein relays signals from outside the cell to the cell's nucleus. These signals instruct the cell to grow and divide (proliferate) or to mature and take on specialized functions (differentiate). It is called KRAS because it was first identified as a viral oncogene in the Kirsten RAt Sarcoma virus. The oncogene identified was derived from a cellular genome, so KRAS, when found in a cellular genome, is called a protooncogene. The gene product of KRAS, the K-Ras protein, was first found
as a p21 GTPase.[6][7] Like other members of the ras subfamily of GTPases, the K-Ras protein is an early player in many signal transduction pathways. K-Ras is usually tethered to cell membranes because of the presence of an isoprene group on its Cterminus. There are two protein products of the KRAS gene in mammalian cells that result from the use of alternative exon 4 (exon 4A and 4B respectively): KRas4A and K-Ras4B. These proteins have different structures in their C-terminal region and use different mechanisms to localize to cellular membranes, including the plasma membrane.

1. KRAS protein: KRAS (Kirsten rat sarcoma 2 viral oncogene homolog) gene is a proto-oncogene that encodes a small GTPase transductor protein called KRAS. KRAS belongs to a group of small guanosine triphosphate (GTP) binding proteins, known as RAS superfamily or RAS-like GTPases. Members of RAS superfamily are divided into families and subfamilies based on their structure, sequence and function. The five main families are RAS, RHO, RAN, RAB and ARF GTPases. The RAS family itself is further divided into 6 subfamilies (RAS, RAL, RAP, RHEB, RAD and RIT) and each subfamily shares the common core G domain, which provides essential GTPase and nucleotide exchange activity. RAS is the most frequently studied proteins in the RAS subfamily. In humans, three RAS genes encode highly homologous RAS proteins, HRAS, NRAS and KRAS. KRAS protein exists as two splice variants, KRAS4A and KRAS4B, in which KRAS4B is the dominant form in human cells.



2. Targeting KRAS signaling in cancer therapy:

Regardless of the tremendous attempts in the past decades that covered the multiple aspects of KRAS activation, KRAS mutant remains being considered as undruggable. As a result, much focus has been put on alternative approaches instead, such as inhibiting signaling cascades downstream of RAS, in particular the MAPK and PI3K pathways. Selective BRAF inhibitors (vemurafenib and dabrafenib) and dual-specificity MEK1/MEK2 inhibitors (trametinib and combimetinib) have been approved to treat BRAF-mutated melanoma alone or in combination. ERK1/2 kinases, as the exclusive downstream of MEK, have attracted intense efforts as well32. Moreover, inhibition of the downstream transcription factors, such as Fos-like antigen 1 (FOSL1), also showed therapeutic promise in KRAS mutant lung and pancreatic cancer33. All these inhibitors could potentially provide therapeutic solutions to a proportion of KRAS mutant cancer but will require.

2.1. Directly targeting mutant KRAS

In principle, it should be possible to design small molecules that directly bind to GTP-binding site on KRAS and inhibit its interaction with GTP, similar to the approach that has been successfully used for the discovery of ATP-competitive inhibitors of protein kinases. 2.2. Targeting KRAS membrane association Previous efforts in this direction primarily focused on targeting KRAS posttranslational8 modifications that modulate KRAS membrane association. 2.3. Exploiting KRAS-regulated metabolic pathways Oncogenic KRAS promotes a metabolic reprogramming of tumor cells, leaning to an anabolic metabolism to produce biomass to support unrest- ricted proliferation. KRAS mutant cancers also use a diverse set of fuel sources to meet their metabolic needs and have developed a variety of mechanisms to obtain metabolic substrates from both extracellular and intracellular sources. 2.4. Synthetic lethality in KRAS mutant cancer For instance, it was lately reported that inhibition of SRC homology region 2containing protein tyrosine phosphatase 2 (SHP2) provokes a senescence response in KRAS-mutant NSCLC, which is exacer- bated by MEK inhibition.

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2.3. Exploiting KRAS-regulated metabolic pathways

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2.5. Immunotherapy for KRAS mutant cancer

cancer immunotherapy is undoubtedly drawing the most attention in cancer treatment at the moment, especially for the immune checkpoint inhibitors that are aggressively tested in almost all cancer types. Recently, these efforts are also gradually expanding to KRAS mutant cancer

3. Molecular Diversity in KRAS Mutant NSCLC Influences Effective Targeting:

KRAS-mutated NSCLC is composed of a heterogeneous set of distinct diseases. Co-occurring genetic events, distinct KRAS mutation subtypes, and mutant KRAS allelic content are among the main drivers that contribute to direct clinical implications. KRAS mutant NSCLC often appears with additional genetic alterations—a feature not shared by other oncogene-driven NSCLC.

Recent RNA sequencing efforts in KRAS+ NSCLC defined three expression clusters dominated by the co-mutations in serine/threonine kinase 11 (STK11, also known as liver kinase B1 (LKB1)) and tumor protein p53 (p53), inactivation of cyclindependent kinase inhibitor 2A/B (CDKN2A/B) and low levels of thyroid transcription factor-1

4. Predictive role of KRAS mutations:

4.1. Predictive value of KRAS mutations for response to chemotherapy

Despite the recent developments in NSCLC therapy, most patients with advanced-stage disease still receive platinum-based chemotherapy. Most studies do not suggest KRAS mutation as a predictive biomarker for response to chemotherapy. The predictive value of KRAS mutation in NSCLC was investigated in the metastatic setting in patients receiving definitive chemotherapy in patients receiving adjuvant chemotherapy with radiation after surgery and also in the phase III TRIBUTE trial where first-line carboplatin/paclitaxel plus erlotinib or placebo was compared in advanced-stage NSCLC. In none of the above settings did KRAS prove to be a predictive factor for response rate, PFS, or OS. More recently, results of the JBR10 trial, which studied the effects of postoperative vinorelbine or cisplatin in patients with resected stage IB or II NSCLC, were published. Remarkable benefit from chemotherapy was only reported in KRAS wild type patients; however, the difference did not prove to be statistically significant ($p = 0.29$). Neoadjuvant and perioperative chemotherapy sequences with carboplatin/paclitaxel or cisplatin/ gemcitabine were compared in the phase III IFCT-0002 trial. KRAS-

mutant tumors were shown to exhibit lower response to cytotoxic chemotherapy in univariate analysis, although KRAS mutation was not a significant predictor in multivariate analysis

4.2. Predictive value of KRAS mutations for response to targeted therapy:

One of the major debates over the predictive role of KRASmutant status of NSCLC patients takes place in the field of EGFRtargeted therapies. Most published data, including a metaanalysis of 22 studies, suggest that KRAS mutational status is a significant negative predictor for EGFR tyrosine kinase inhibitors (TKIs). Accordingly, KRASmutated patients treated with EGFR TKIs have a trend for worse objective response rates (ORR), PFS, and OS compared with patients without KRAS mutation.

However, despite the convincing results, controversies still exist and not all studies have reached the same conclusions

4.4. Predictive value of KRAS mutations for response to immune checkpoint inhibition therapy:

Programmed cell death protein 1 (PD-1) expression has been shown to be in close connection with KRAS status, and KRAS mutations were described as possible biomarkers for immune checkpoint inhibitors. Also, a clinical benefit was reported to PD-
1 inhibitors in KRAS-mutant patients.

5. KRAS as a therapeutic target in NSCLC

5.1 Pitfalls of KRAS mutation targeting in NSCLC:

Because of its high mutation frequency in NSCLC, KRAS is an appealing target. However, the development of targeted therapies for KRAS-mutant lung cancers has long been marked by frustration. For decades, KRAS was considered undruggable due to its exceptionally high affinity to GTP/GDP, to the absence of known allosteric binding sites, and to the presence of extensive posttranscriptional modifications. KRAS protein shows high resistance against smallmolecule modulation, since it is a small protein with a relatively smooth surface without clear binding pockets (besides its GTP/GDP binding pocket). Under physiological conditions in vivo, GTP almost exclusively occupies all potential binding sites with extremely high affinity.

5.2 Targeting KRAS membrane anchorage:

KRAS proteins require membrane associations to become biologically active. The membrane anchorage of KRAS is dependent on posttranslational modification of the CAAX motif by farnesyltransferases. Initial preclinical studies with farnesyltransferase inhibitors (FTIs) demonstrated moderate success in blocking tumor cells both in vitro and in vivo. However, in the presence of FTIs, KRAS can be alternatively prenylated by geranylgeranyl-transferase-I, thus overcoming the effect of farnesyltransferase inhibition. As expected, these results foreshadowed the disappointing clinical trials with FTIs that failed to improve outcomes in KRASmutant LADC patients. Still, some novel FTIs, when combined with other inhibitors such as geranylgeranyltransferase inhibitors, showed potent anti-cancer activities in KRAS-driven pancreatic tumors.

Nevertheless, the efficacy of these dual-functional therapeutic agents has not yet been investigated in LADC

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5.3 Targeting KRAS downstream signaling pathways:

Another feasible approach to treat KRAS-mutated NSCLC might be to target the main signaling pathways controlled by the constitutively active mutant KRAS (i.e., the RAF-MEKERK or the PI3K/AKT/mTOR pathways). The inhibitors of these signaling pathways have been tested in different RASdriven tumor types, and some of them showed promising activity in preclinical models. The results of conducte.

5.4 Synthetic lethal vulnerabilities in KRAS-mutant NSCLC.

An alternative approach to direct targeting of KRAS-mutant cancer genes involves targeting co-dependent vulnerabilities or synthetic lethal partners that are preferentially essential for KRAS oncogenesis. The therapeutic ablation of these secondary targets would hypothetically result in the selective death of KRASmutant but not KRAS wild type tumor cells.

5.6 Direct targeting of mutant KRAS

KRAS has been historically acknowledged a non-druggable target. However, according to the results of the latest preclinical findings, the landscape of G12C KRAS-mutated lung cancer might change. After the discovery of new allosteric regulatory pockets in GDP-RAS adjacent to the cysteine residue of KRAS G12C, compounds nucleotide-binding pocket (SML-8-73-1) or allele-specific inhibitors (ARS-853) have been reported. Of note, the effects of both SML-8-73-1 and ARS-853 on mutant KRAS G12C are irreversible. SML-8-73-1 can covalently react with KRAS G12C, thus competing with GTP and GDP for active site binding in a cellular context even in the presence of a very high concentration of GTP. Accordingly, by locking the KRAS-GDP state, these GDP-derived inhibitors can block the proliferative activity of the KRAS-mutant cells. Despite their preclinical

6 Open questions and future challenges:

While direct KRAS G12C inhibitors have shown promising results in some solid tumors including LADC, the development of new potential therapeutic strategies for the treatment of KRAS-mutated lung cancer is a work in progress, and many questions remain. 1. Despite the promising results achieved with direct KRAS G12C inhibitors, approximately half of the G12Cmutant lung cancer patients show only a partial response to these therapeutic agents. The mechanism of how cancer cells bypass inhibition to prevent maximal response to therapy is not yet fully understood. A possible explanation might be that some quiescent cells produce new KRAS G12C in response to suppressed mitogen-activated protein kinase output

which is maintained in its active, drug-insensitive state by the epidermal growth factor receptor and aurora kinase signaling. Since the inhibitors bind only to the inactive conformation of KRAS, the cells with these adaptive changes bypass the effects of KRAS G12C inhibitors and resume to proliferate

1. Conclusions

2. To summarize, although KRAS mutations represent one of the most common oncogenic driver mutations in lung cancer, KRAS has been historically acknowledged a non-druggable target. Indeed, to date, no effective RAS inhibitors are used in routine clinical practice. Furthermore, the predictive role of KRAS mutation in patients receiving chemo-, targeted, antivascular, or immunotherapy needs to be clarified. Nevertheless, recent data on the novel direct covalent KRAS G12C inhibitors AMG 510 and MRTX 849 appear to be promising both in preclinical and clinical settings. Other therapeutic approaches such as combinatory therapy with targeted agents, immune checkpoint inhibitors, KRAS downstream inhibitors, or the newly developed direct covalent inhibitors are also encouraging but require further clinical testing. At the same time, mechanisms of adaptive resistance that limits the therapeutic potential of conformation-specific KRAS G12C inhibition might represent a possible future challenge that must be overcome for durable responses. All in all, despite the historical lack of progress, the emergence of new promising agents might change the therapeutic landscape of KRASmutant LADC.

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