Review Article

# KRAS mutant NSCLC, a new opportunity for the synthetic lethality therapeutic approach

**Javier de Castro Carpeño[1], Cristóbal Belda-Iniesta[2]**

[1]Medical Oncology Unit, Department of Translational Oncology, Hospital Universitario La Paz, idiPAZ, Madrid, Spain; [2]Thoracic, H&N and Neuro-oncology Unit, CIOCC, GHM, Madrid, Spain

*Corresponding to:* Dr. Javier de Castro Carpeño. Medical Oncology Unit - Department of Translational Oncology, Hospital Universitario La Paz, Paseo de la Castellana, 261, 28046 Madrid (Spain). Email: javier.decastro@salud.madrid.org.

**Abstract:** K-RAS accounts for 90% of RAS mutations in lung adenocarcinomas, the most commonly mutated oncogene in NSCLC, with mutations detected in about 25% of all tumors. Direct inhibition of KRAS has proven clinically challenging. So far, no successful targeted therapy has been developed and remains an elusive target for cancer therapy. Despite significant efforts, currently there are no drugs directly targeting mutated KRAS. Thus, new strategies have emerged for targeting RAS including the use of synthetic lethality.

A specific knowledge of individual tumor molecular abnormalities that result in oncogene-specific "synthetic lethal" interactions will allow the rationale to combine promising targeted therapies for KRAS-mutated NSCLC. In this article, we review the new approach based on testing drugs or combinations of agents that work downstream of activated K-RAS.

**Key Words:** RAS oncogene family; KRAS mutant; NSCLC; selumetinib; synthetic lethality

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## Introduction

Lung cancer is the leading cause of cancer deaths worldwide and non–small cell lung cancer (NSCLC) accounts for 80% of all lung cancer cases (1). The standard first-line therapy for patients with advanced NSCLC was a platinum-based doublet combination chemotherapy but modest progress has been made with the use of chemotherapy, and additional treatment strategies are needed. So cancer drug development has shifted from cytotoxic, nonspecific chemotherapies to molecularly targeted, rationally designed drugs with greater efficacy and lower toxicities. For this challenge, the best knowledge of cancer biology is required. Nowadays, we are able to identify different genetic changes that allow us to consider NSCLC as a major disease which can be molecularly reclassified into several subsets of diseases (2). RAS gene family members encode small GTPases that activate various signaling pathways involved in proliferation, differentiation and cell survival (*Figure 1*). RAS proteins function as molecular switches that cycle between a GDP-bound inactive state and GTP-bound active state. Ras proto-oncogenes are the most frequent mutated genes in NSCLC, with mutations detected in about 25% of all tumors, mainly adenocarcinoma subtype (3).

v-Ki-ras2 Kirsten rat sarcoma viral oncogene (K-RAS) accounts for 90% of RAS mutations in lung adenocarcinomas. Most oncogenic forms of RAS impair their intrinsic GTPase activity, preventing GTP hydrolysis.

RAS proteins acquire the potential to transform the cells when an amino acid at position 12, 13, or 61 is replaced as a result of a point mutation in the gene but 97% of K-RAS mutations in NSCLC involve codons 12 or 13 at P-Loop also known as Walker A motif. This domain interacts with the phosphate group of GTP helped by GAP protein. In this regard, mutations at codon 12 avoid K-Ras to be stimulated by GAP protein. As GAP acts as a catalyst to

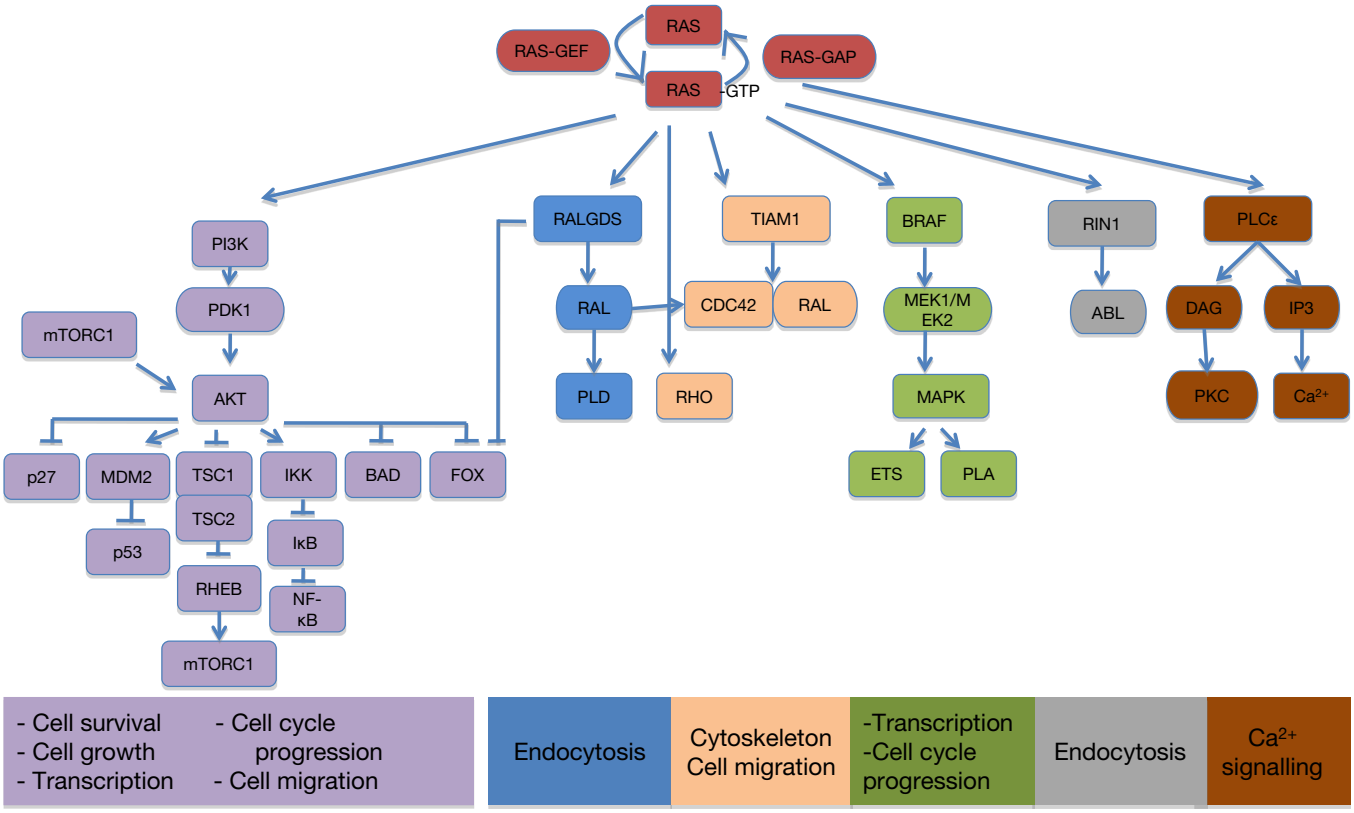


**Figure 1** The major RAS effector pathways. CDC42, cell division cycle 42; DAG, diacylglycerol; FOX, forkhead transcription factor; GAP, GTPase-activating protein; GEF, guanine nucleotide exchange factor; IKK, IκB kinase; IP3, inositol-1,4,5-trisphosphate; mTORC, mTOR complex; NF-κB, nuclear factor-κB; PDK1, phosphoinositide-dependent kinase 1; PKC, protein kinase C; PLA, phospholipase A; PLCε, phospholipase Cε; PLD, phospholipase D; RALGDS, RAL guanine nucleotide dissociation stimulator; RHEB, RAS homologue enriched in brain; RIN1, RAS and RAB interactor 1; TIAM1, cell lymphoma invasion and metastasis 1

speed up GTPase activity, mutations at that position slow GTP transition to GDP increasing GTP levels. Mutations at codon 61 affect the energy gradient needed to transform substrate (GTP) into product (GDP) because wild-type residue at that position stabilizes the transition state for GTP hydrolysis. So, it is critical to know specific site and biochemical effects when a K-Ras mutation is diagnosed because pharmacological modulation is completely different.

Although KRAS mutations have been widely hypothesized to be related to direct tobacco exposure, they do occur in approximately 15% of lung adenocarcinomas from never-smokers (4). Thus, KRAS tumor status cannot be easily predicted on the basis of smoking history alone. KRAS transversion mutations (G/TorG/C) are more common in former or current smokers and transition mutations (G/A) are more common in patients who never smoked cigarettes.

KRAS mutations have been associated with a poor prognosis such as a lower expectancy for survival (5), reduced benefit from adjuvant chemotherapy, they predict resistance towards EGFR tyrosine kinase inhibitors (6), and obtain less clinical benefits from chemotherapy compared with the general NSCLC population (7).

## Treatment of KRAS mutated NSCLC: an unresolved issue

Direct inhibition of KRAS has proven clinically challenging. Although KRAS mutations were identified in lung cancer nearly 30 years ago (8), no successful targeted therapy has been developed and remains an elusive target for cancer therapy (9). So far, there is no yet effective treatment for patients with these types of tumors although we consider that K-RAS is not a unique target but a myriad of targets that combine absence of affinity for a catalyst (GAP) or

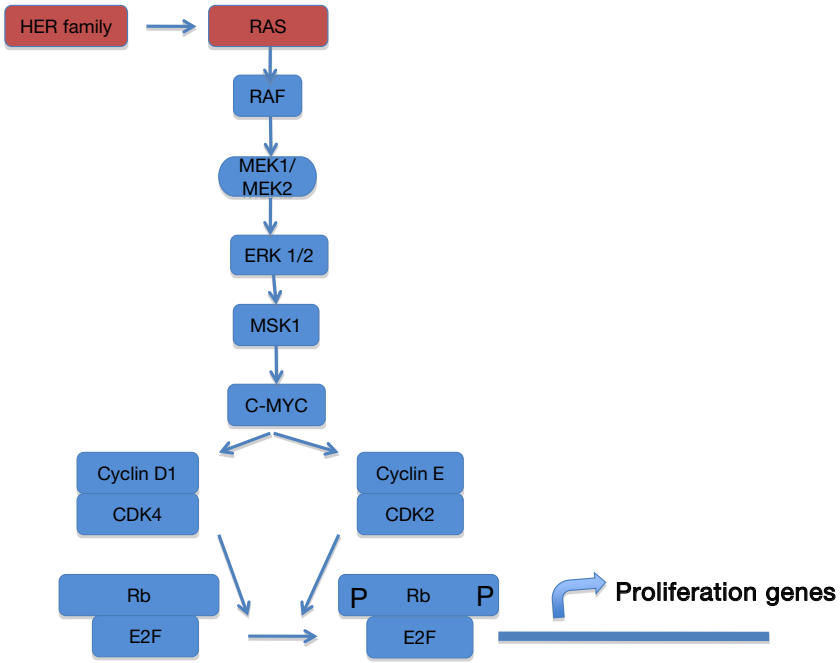


**Figure 2** The relationship between HER family, KRAS and cyclin-dependent kinases (Cdk)

decreasing affinity for GTP (P-Loop impairing) as well as other biochemical complexities.

Until now, all efforts to inhibit mutant KRAS in NSCLC have failed and few compounds have been assessed by clinical trial. One of the reasons to explain this point is because RAS enzyme kinetics is hard to inhibit due to affinity to substrates, catalyst proteins and sequential conformational changes after first signal that occurs inside this multi-target protein. In fact, the lack of specificity of KAS inhibitors could be related to this biochemical complexity that could be targeted at different levels: membrane attachment, P-Loop and thermodynamic requirements.

Various potent and selective inhibitors of RAS function were developed in the 1990s, with the aim to prevent association of RAS with the inner face of cell membrane (10). First, farnesyl transferase inhibitors avoid a critical post-translational modification in pre-RAS protein blocking isoprenylation. As farnesyl residues are needed to attach K-RAS to membrane it was hypothesized that this sort of inhibitors could inhibit RAS proteins (11). In fact, these inhibitors blocked RAS-dependent oncogenic activity "*in vitro*" and in preclinical animal models, but unfortunately failed in the clinical practice and showed little clinical efficacy because of a sequential post-translational modification at pre-Ras that compensates first steps of K-RAS maturation (12).

Although effective KRAS inhibitors are not currently available, genetic approaches have identified novel drug targets that are essential for RAS cellular localization and function, raising hope that new inhibitors of specific biochemical functionality of K-RAS will soon be developed.

## Rationale for a new treatment strategy for K-RAS mutated NSCLC

A different approach has been based on testing drugs or combinations of agents that work downstream of activated K-RAS. If you take into account that different KRAS-mutant tumors can activate several signalling pathways, a new treatment strategy for KRAS-mutant NSCLC should be based on the combination of targeted agents that inhibit downstream effectors of K-RAS dependent-tumors according to the "RAS-ome" (*Figures 2,3*). In this way, a specific knowledge of individual tumor molecular abnormalities that result in oncogene-specific "synthetic lethal" interactions will allow the rationale to combine promising targeted therapies for KRAS-mutated NSCLC.

### *Targeting HER pathway*

Epiregulin (EREG) is ligand of the EGF receptor/EGFR and ERBB4 and is a putative transcriptional target of

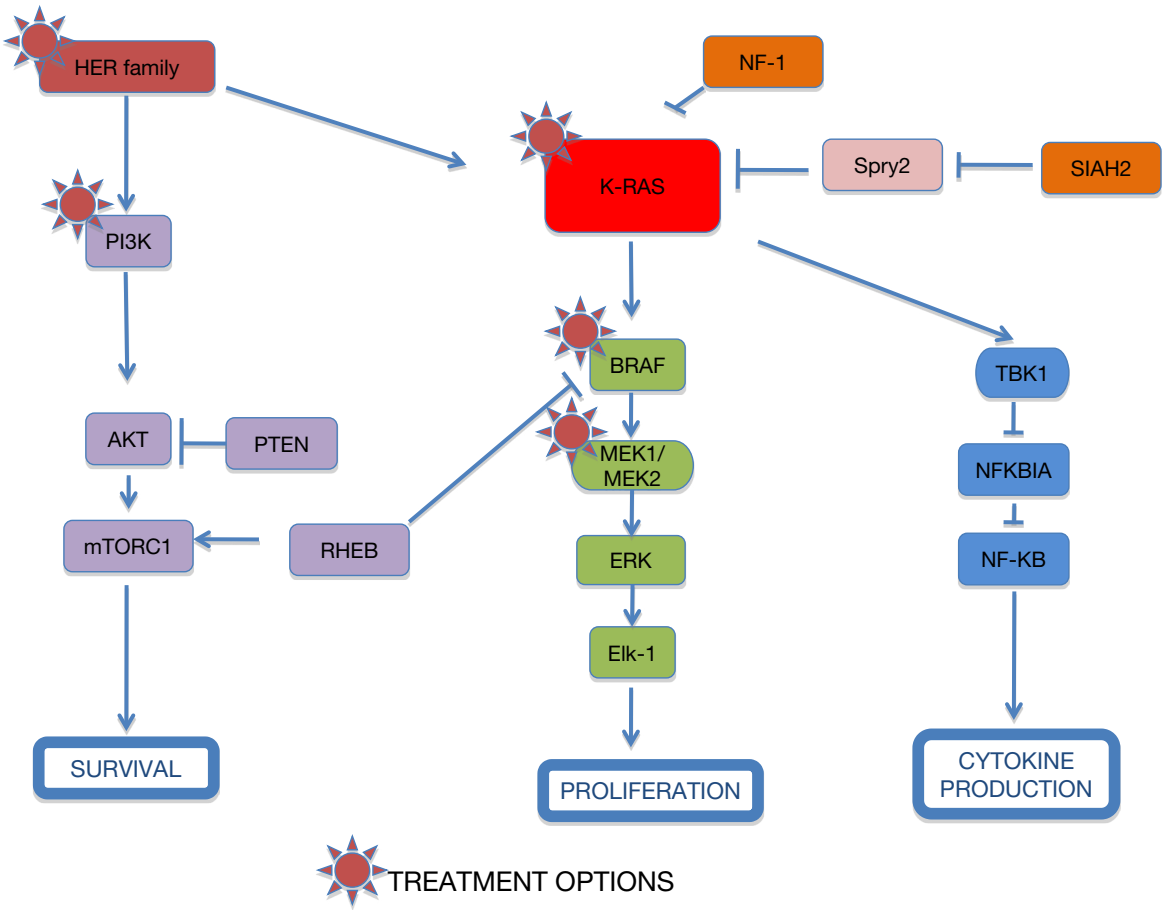


**Figure 3** Major interactions in the KRAS pathway

mutated KRAS dependent signaling that contributes to an aggressive phenotype and could be a promising therapeutic target in oncogenic KRAS-driven NSCLC (13) (*Figure 2*).

### *Targeting MEK pathway*

Initial efforts focused on proteins downstream K-Ras at the RAS/RAF/mitogen-activated protein kinase (MEK)/extracellular signal-regulated kinase (ERK) signaling pathway. The MAPK pathway converges at the MEK1/MEK2 kinases, for which the only known substrates are the ERK1/ERK2 kinases (*Figures 2,3*). In fact, MEK inhibition would block ERK signalling irrespective of the upstream stimulus.

MEK1 and MEK2 are dual specificity kinases, RAF-phosphorylated, that phosphorylate the tyrosine and threonine residues on ERK1 and 2, leading to proliferation and migration activation. Mutations in RAS or RAF lead to a sustained oncogenic signal and predict response to MEK inhibition in laboratory models.

Selumetinib (AZD6244, ARRY-142886; AstraZeneca, Alderley Park, Cheshire, UK) is an orally available, potent, selective, non-ATP competitive inhibitor of MEK1/MEK2 kinases (IC50 14 nM for MEK1). Preclinical data from KRAS-mutant NSCLC tumor xenografts showed that selumetinib significantly suppressed tumor growth (14), especially in tumors harboring RAS mutations (15). Initial clinical studies of selumetinib showed target inhibition and tumor responses (16). A phase I trial demonstrating tolerability and preliminary efficacy of selumetinib at 100 mg twice daily (17), identified an acneiform rash as the main dose-limiting toxicity (DLT). However, treatment with selumetinib alone, showed little clinical efficacy in a phase II clinical trial in unselected pre-treated patients with NSCLC when selumetinib was compared with pemetrexed (18).

Results of additional preclinical *in-vivo* studies have shown that the combination of selumetinib and docetaxel leads to greater tumor-growth inhibition or regression, and

apoptosis (19,20). This combination showed a manageable tolerability profile in advanced solid tumors (21) in phase I. With this rationale, a randomised, double-blind, phase II clinical trial combining docetaxel (75 mg/m$^2$ on day 1 of a 21-day cycle) with or without oral selumetinib (75 mg twice daily in a 21-day cycle) in KRAS-mutant NSCLC patients after first-line progression (22). Mature data evidenced a promising trend in overall survival for patients treated at experimental arm (median OS 9.4 *vs.* 5.2 mo; HR 0.80; 80% CI, 0.56-1.14; one-sided P=0.21). Additionally, median progression-free survival was statistically significant (5.3 *vs.* 2.1 mo, HR 0.58; 80% CI, 0.42-0.79; one-sided P=0.014), and an impressive response rate around 37% in the combination group compared with 0% in the docetaxel alone group (P<0.0001). In post-hoc analyses, there were also improvements in lung cancer symptoms and all these benefits might be attributable to the cytoreductive effects of the treatment. However, a higher rate of febrile neutropenia (18% *vs.* 0%), diarrhea, vomiting, stomatitis, and dry skin with selumetinib plus docetaxel were communicated.

Obviously, this is a phase II study and requires further validation in a large phase III clinical trial. Furthermore, the study has potential limitations such as the small sample size and the absence of independent confirmation of progression-free survival and tumor response. Moreover, the control group of the study who received docetaxel alone clearly had poor evolution, lower than expected in previous clinical trials in unselected patients receiving docetaxel at second line setting (23). Furthermore, a new question emerges because poor efficacy of docetaxel in K-RAS mutant NSCLC patients should be investigated. Conversely, the potential synergy of docetaxel and selumetinib remains unclear and additional studies are needed. *In-vivo* mechanistic drug sequencing studies have shown that administration of selumetinib after docetaxel, rather than before, induced more apoptosis. This finding could have important clinical implications for any dosing schedule of this combination. This contrasts with the majority of previous studies in NSCLC, in which addition of a targeted agent to chemotherapy has not resulted in improved efficacy.

Another important issue is the therapeutic effect of specific KRAS mutations, to define a subpopulation of KRAS-mutant NSCLC in which the combination of selumetinib and docetaxel leads to improved efficacy. Previous studies showed that KRAS mutation subtype seems to be an important predictor of treatment outcome (24).

Wide genomic approaches have evidenced that it is usual for many mutations to co-exist. In this regard, K-RAS mutations in NSCLC patients could be co-expressed with additional sequence alterations. Thus, a recent study done in mice showed that overlapping mutations at p53 or LKB1 affect efficacy of selumetinib plus docetaxel (25) as well as docetaxel alone in tumors that harbors a mutated Kras sequence. For example, combination of selumetinib plus docetaxel provides substantial benefit in K-Ras$^{mt}$/p53$^{mt}$ lung cancer models. Conversely, mice harboring Kras$^{mt}$/LKB1$^{mt}$ tumors show primary resistance to this schedule. LKB1 (liver kinase B1) also known as serine threonine kinase 11 (STK11) the defective sequence of which is a cause of Peutz-Jeghers syndrome. Its role is critical in p53-dependent apoptosis, mainly involved at mitochondrion steps. When LKN1 is unable to exert its activity, p53-dependent death is impaired. LKB1 is somatically inactivated in about 30% of NSCLC (26), and the combination of LKB1 loss and KRAS mutation results in a more aggressive phenotype than tumors only harboring KRAS mutations (27). In fact, the decreased activation of ERK phosphorylation in KRAS/LKB1 tumors suggests that the proliferation of these tumors may be driven through other signaling pathways. KRAS/LKB1-mutant tumors have heightened activation of both AKT and SRC. This type of tumors with KRAS mutated and LKB1 inactivated show sensitivity to rapamycin or the MEK inhibitor CI-1040.

Several selumetinib trials are currently enrolling patients, including a phase II study (NCT01229150) in previously treated NSCLC stratified by KRAS status. Mutated KRAS and wild-type KRAS patients are randomized to receive selumetinib and erlotinib or selumetinib alone (28). In addition, the drug is being evaluated with thoracic radiation in one trial (NCT01146756) and in two multi-arm trials (NCT01306045 and NCT01248247) that assign treatment by molecular tumor characteristics.

Other MEK inhibitors have been already tested. Trametinib (GSK 1120212 or JTP-74057) is a reversible, allosteric MEK1/MEK2 inhibitor with an IC50 of 0.7 nM for MEK1, and a high specificity as demonstrated by limited activity against a panel of 180 other kinases. A multi-arm phase I/Ib trial (NCT01192165) is assessing many treatment combinations, specifically with a goal of identifying appropriate regimens for lung and pancreatic cancer treatment. An open-label, randomized phase II trial (NCT01362296) in second-line NSCLC that harbors muta¬tion in KRAS, NRAS, BRAF, or MEK1 is currently recruiting patients.

Dual targeting of MEK with inhibition of other kinases in the same pathway, such as EGFR, or with inhibition

 

of a parallel pathway are also promising directions for ongoing trials.

### *Targeting PI3K pathway*

PI3K is a site of convergence and stem for multiple pathways resulting in complex regulation of signaling and the potential for significant off-target effects, including activation of alternative networks to promote oncogenesis (*Figure 3*).

NSCLC harbors several molecular alterations involving the PI3K pathway, including PIK3CA amplification and mutation, decrease or loss of phosphate, and tensin homologue (PTEN), AKT mutations, LKB1 loss and KRAS mutation. For all of these features, PI3K pathway is one of the promising approaches to target RAS downstream signaling proteins. Conversely, K-RAS mutations have been predicted to mediate resistance to PI3K inhibitors (29). For this reason, a potential strategy of treatment of KRAS mutant tumors will be focused on dual inhibition of PI3K and MEK/ERK signaling.

MK-2206 is an oral pan-Akt inhibitor that binds Akt in its inactive configuration. MK-2206 has shown preclinical activity in a panel of NSCLC lines, with the greatest activity in a PIK3CA-mutated model (30). Combination therapy with selumetinib demonstrated synergy (31) and is being evaluated clinically (NCT01021748) (32).

### *Targeting nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB) pathway*

KRAS mutated tumors can activate nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB) pathway and produce anti-apoptotic signals, essential for NSCLC survival through cREL and Bcl-xL (33) (*Figures 1*,*3*). So, NF-κB signaling and the non-canonical IκB kinase, TBK1, may represent an alternative strategy for targeting $KRAS^{mt}$-driven tumors. These observations suggest a pharmacological alternative for potential treatment of cancers harboring RAS mutations (34).

### *Neurofibromatosis type 1 pathway*

Neurofibromatosis type 1 (NF1) gene regulates cell motility and invasion, and displays high homology with RAS GTPase activating protein (*Figure 3*). Loss of NF1 produces hyper-activation of RAS signaling in 40% of NSCLC (35). NF1-deficient malignancies and KRas/p53-mutant lung cancer exhibit an aggressive phenotype in murine models. However, agents that enhance proteotoxic stress, including the HSP90 inhibitor IPI-504 showed relevant responses when combined with rapamycin (36). Other HSP90 inhibitors are under evaluation (37). Since the mTOR inhibitor rapamycin has shown potential activity against NF1-associated tumors, it could be a new option of treatment (38).

### *Wilms tumor gene pathway*

The Wilms Tumor gene (WT1) is a tumor suppressor gene that recognizes and binds to the DNA sequence 5'-CGCCCCCGC-3'. Curiously, function may be isoform-specific as isoforms lacking the KTS motif may act as transcription factors and isoforms containing the KTS motif may bind mRNA and play a role in mRNA metabolism or splicing. This biological complexity offers many possibilities for drug development, including those that affect $KRAS^{mt}$ driven biology. Recently, a study in both mouse and human cells has shown that the loss of WT1 could activate a senescence program in $KRAS^{mt}$ cells (39). If this observation is confirmed, a new approach of treatment will be opened.

### *GATA2 pathway*

The development of RNA interference technology has enabled the possibility of testing biological roles of putative genes in wide-genome scale. In this regard, several screenings assays have been carried out in cell libraries aimed to identify genes the inhibition of which is selectively deleterious to $K\text{-}RAS^{mt}$ cells (40). Candidate genes were then tested in larger panel of KRAS mutant and wild-type cancer cells. Finally, $K\text{-}RAS^{mt}$ cancer cell lines were found to be dependent on some genes such as the transcription factor GATA2 (41).

GATA-binding Factor 2 or erythroid transcription factor (GATA2) can be involved in regulation of the proteasome activity, IL-1 and Rho-signaling pathways. Recently, it has been observed that loss of GATA2 reduced the viability of NSCLC cells harboring RAS mutations, whereas wild-type cells were unaffected (42). Although GATA2 itself is likely undruggable, combined suppression of GATA2-regulated pathways with clinically approved inhibitors caused marked tumor clearance. Pharmacological inhibition of GATA2-mediated pathways with bortezomib and fasudil results in dramatic tumor inhibition (43). These observations present a new treatment option to KRAS mutant NSCLC.

 

### *Seven in absentia homolog 2 pathway*

The human homolog of Drosophila seven-in-absentia--SIAH-1 and SIAH-2 are ubiquitin E3 ligases and driving ubiquitin-mediated degradation of conserved downstream components of the RAS pathway that are required for mammalian RAS signal transduction (*Figure 3*). In this regard, SIAH-2 regulates the tumor growth by degradation of SPRY2 and subsequent activation of the RAS-ERK pathway. Since SIAH-2 can be involved in different NSCLC, SIAH-2 may be a viable target for novel anti-RAS and anticancer agents aimed at inhibiting EGFR and/or RAS-mediated tumorigenesis (44).

### *RNA-binding motif 5 pathway*

RBM5 (RNA-binding motif protein 5, also named H37/LUCA-15) gene is a component of the spliceosome. A complex (also known as the prespliceosome) that regulates the alternative splicing of a number of mRNAs. It has demonstrated tumor suppressor activity (45). RBM5 can inhibit the growth of lung cancer cells and induce apoptosis both *in vitro* and *in vivo* (46). RBM5 is downregulated by the constitutively activated RAS mutant protein, RAS (G12V), in rat embryonic fibroblast cells, which indicates a correlation between the RAS pathways and RBM5 activity (47). Further evaluation of interrelationships between RBM5 expression and KRAS gene must be carried out to open a novel therapeutic approach.

### *IL-8 pathway*

Interleukin-8 (IL-8; CXCL8) is a cytokine of the CXC chemokine family that is involved in neutrophil recruitment and activation. In addition, IL-8 is an angiogenic growth factor that is overexpressed in different cancers, including NSCLC (48). Lung adenocarcinoma and muco-epidermoid carcinoma cells produce substantial amounts of IL-8, and express both CXCR1 and CXCR2 IL-8 receptors. Activating mutations of KRAS upregulate IL-8 expression in NSCLC and IL-8 can play a role in cell growth and migration in oncogenic KRAS-driven NSCLC (49).

### *Twist-related protein 1 pathway*

Twist1 acts as a transcriptional regulation as a heterodimer with E proteins. Interestingly, Twist1 regulates gene expression differentially, depending on dimer composition: homodimers induce expression of FGFR2 and POSTN while heterodimers repress FGFR2 and POSTN expression and induce THBS1 expression. Additionally, it has been suggested to play an important role during tumor progression. For example, transgenic mouse models have shown that Twist1 cooperates with KRAS (G12D) to markedly accelerate lung tumorigenesis by abrogating cellular senescence programs and promoting the progression from benign adenomas to adenocarcinomas. Moreover, the suppression of Twist1 to physiological levels is enough to cause KRAS mutant lung tumors to undergo senescence losing their neoplastic features (50). The suppression of TWIST1 in human tumors may be an effective example of pro-senescence therapy.

## Conclusions

Traditionally, treatment decisions for patients with lung cancer have historically been based on tumor histology and TNM stage. One promising treatment strategy involves the further subdivision of NSCLC into clinically relevant molecular subsets, according to a classification schema based on specific so-called driver mutations.

Although mutational activation of the KRAS pathway is the most frequent genetic event in NSCLC, it remains an elusive target for cancer therapy. In fact, it has been considered an "undruggable" genetic alteration.

A key goal in cancer research is the discovery of new drug targets that will selectively impair the viability of tumoral cells such as KRAS mutant NSCLC. Therefore, a specific knowledge of individual tumor molecular abnormalities that result in oncogene-specific "synthetic lethal" interactions will allow the rationale to combine promising targeted therapies for KRAS-mutated NSCLC. Recently, a MEK inhibitor, selumetinib, has shown interesting efficacy when combined with docetaxel in patients with KRAS-mutant tumors. Several pathways may provide attractive approaches to develop new treatments in KRAS-mutated NSCLC.

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