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Review Article

Therapeutic Approaches of Non-Small Cell Lung Cancer (NSCLC) with *KRAS* Mutations

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Abstract

Mutations in *KRAS* are among the most commonly observed mutations in Non-Small Cell Lung Cancer (NSCLC) patients. However, different therapeutic approaches targeting mutant *KRAS* so far were not efficient. Targeting *KRAS* downstream signaling pathways such as MAPK, ERK is a promising tool to control the disease. In the current review, the different therapeutic strategies are briefly discussed.

Keywords: Non-small cell lung cancer; *KRAS* mutations; Therapy

Introduction

Lung cancer is associated with the highest cancer-related mortalities all over the world [1]. Several oncogenic mutations have been linked to the development of lung cancer. *KRAS* mutations are among those mutations that exist in about quarter of Non-Small Cell Lung Cancer (NSCLC) patients [2]. Mutations in Epidermal Growth Factor Receptor (EGFR) have also been observed in NSCLC patients. Mutations in *EGFR* and *KRAS* have been shown to be mutually exclusive in patients with NSCLC [3]. However, double mutations have recently been reported in some cases [4]. *KRAS* mutations can also coexist with other mutations such as p53and *STK*11 [5,6].

RAS is a GTP kinase that has been discovered almost 60 years ago. In NSCLC, *KRAS* missense substitutions mutations are mainly observed at codon 12, codon 13, and to a lesser extent at codon 61 [7]. G12C is the main *KRAS* mutation found in lung cancer patients that accounts for about 40% and is mostly observed in smokers. Other mutations include G12V and G12D that account for 22% and 16% of mutations, respectively [8,9]. The available information regarding the prognostic significance of *KRAS* mutations in NSCLC patients are scarce and elusive. In an earlier report, NSCLC patients with *KRAS* mutations has been shown to have a shorter overall survival (OS) compared to patients with wild-type *KRAS* [10]. In another study conducted on patients treated with first-line platinum-based chemotherapy, *KRAS* mutations have been shown to mildly affect OS [11]. However, in a recent study, analysis of data from patients treated with EGFR-tyrosine kinase inhibitor failed to demonstrate any difference in survival between wild-type and mutant *KRAS* tumors [12]. Moreover, *KRAS* mutation has recently been shown to be associated with poor prognosis in patients with lung adenocarcinoma with bone metastasis [13]. The type of mutated codon could also affect the disease outcome [9]. Codon 12 mutation, G12V, has been shown to be associated with poor prognosis [10,14].

Similar to its prognostic value, the predictive role of *KRAS* mutations in response to chemotherapy is also contradictory. Several studies did not show any predictive role of *KRAS* mutations in efficient response to chemotherapy [15-17]. A recent meta-analysis conducted on patients with advanced NSCLC following first line chemotherapy demonstrated that *KRAS* mutations decreased Overall Response Rate (ORR) and Progression Free Survival (PFS) [18]. An earlier retrospective analysis demonstrated a limited role of *KRAS* mutation in Asian patients with advanced NSCLC [19].

G12C and G12V mutations activate several downstream signaling cascades including RAL pathway and thus are associated with poor prognosis [20]. On the other hand, G12D mutation induces RAF/MAPK/PI3K signaling [20]. Collectively, mutations in *KRAS* result in constitutively active protein independent of upstream signals due to loss of GTPase activity with subsequent activation of several downstream pathways such as MAPK, and AKT/mTOR. Therefore, targeting these signaling pathways is the preferred approach to treat lung cancer patients with *KRAS* mutations.

RAS Signaling

In normal cells, RAS is usually inactive and bound to GDP until it is triggered by external stimuli that exchange GDP for GTP forming an active molecule. Consequently, GTPase activating proteins inactivate RAS through hydrolysis of GTP. Mutations in *KRAS* are associated with loss of GTPase activity leading to constitutively active protein [21]. The signaling pathways downstream of *KRAS* (Figure 1) are in turn switched on including MAPK, ERK, AKT/mTOR leading to increased proliferation, angiogenesis, and resistance to apoptosis that favors tumor growth [21].

KRAS-Targeted Therapeutic Approaches

Most of therapeutic strategies that were developed to treat NSCLC patients with *KRAS* mutations are targeting its downstream signaling pathways such as RAF, MEK, ERK, PI3K. However, thorough understanding of these signaling pathways is crucial before developing therapeutic agents. For instance, MEK is activated by RAF, which in turn activates ERK that stimulates several downstream targets including transcription factors and protein kinases responsible for resistance of apoptosis, cell invasion, proliferation, and cell cycle progression [21]. Therefore, it is a real challenge to identify which arm in the signaling pathway is needed to be targeted to inhibit tumor progression. In addition, understanding of the main signaling pathways driven within the context of different *KRAS* mutations is indispensable for developing effective therapeutic strategies of NSCLC patients [21-23]. Over the past twenty years, several therapeutic

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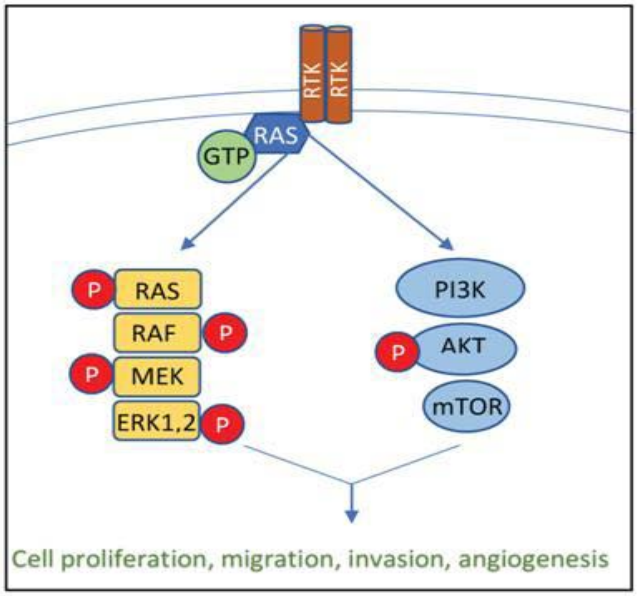

Figure 1: *KRAS* signaling in NSCLC. Mutations in *KRAS* are associated with a constitutively active RAS protein with the induction of downstream signaling cascades such as MEK/ERK1, 2 and PI3K/AKT/mTOR pathways that leads to proliferation, migration, invasion, and angiogenesis.

agents against *KRAS* have been tested either by using pharmacologic inhibitors or its downregulation by siRNA. In addition, targeting *KRAS* downstream signaling pathways has also been examined.

Different strategies have been developed to target activated oncogenic GTP-RAS protein. First, by a competitive inhibitor that interferes with *KRAS* interaction with GTP [24-27]. The other approach was by targeting membrane binding of RAS [28]. However, inhibiting the membrane localization of RAS by an inhibitor, salirasib, was not efficient in phase II clinical trial [29]. A prospective trial study conducted in 2011 showed a remarkable effect of sorafenib treatment of NSCLC patients with *KRAS* mutation than those treated with erlotinib [30]. However, due to its toxicity, it is uncertain that sorafenib will be a good therapeutic agent for NSCLC patients with *KRAS* mutations.

Recently, a small inhibitor molecule that specifically binds to G12C mutant *KRAS* with no effect on wild-type protein has been developed that renders mutant protein to bind GDP instead of GTP [27]. That pre-clinical finding could pave the road to develop a second generation of the inhibitor to be used for phase I or phase II trials.

Immunotherapy

Immunotherapy is considered as a breakthrough therapeutic approach for cancer. The recent advanced immunotherapeutic strategies are based on the inhibition of protective mechanisms employed by cancer cells against immune cells. This is achieved by blocking certain immune checkpoints, such as Programmed cell Death-1 (PD-1). Recently, targeting PD-1 and its ligand PDL-1in clinical trials has demonstrated exceptional responses in NSCLC patients [31,32]. However, the response to immunotherapy is currently limited to a small number of patients [33]. Interestingly, It has recently been shown that patients with lung adenocarcinoma with *KRAS* and or/TP53 mutations exhibited more sensitivity to PD-1 targeted immunotherapy [34]. These findings suggest a potential predictive significance of *KRAS* mutation in immunotherapy.

Alternative Therapeutic Approaches

Since targeting *KRAS* has been shown to be inefficient, an alternative approach by inhibiting its downstream target such as MAPK could be more effective. Therefore, using sorafenib, a multidrug TKI, in a phase II trials was promising in controlling the disease [30,35,36]. However, in phase III MISSION trial, the analyses of group with *KRAS* mutations did not show any effectiveness of sorafenib [37].

Another candidate downstream of RAS is MEK1/2. An oral non-ATP competitive MEK1/2 inhibitor, selumetinib was developed [38]. Treatment of advanced cancer patients with that inhibitor achieved a good tumor response in early phase [39]. However, it showed little effect in phase II trials [40]. Combined treatment of selumetinib and docetaxel exhibited a good synergistic tumor regressive effect *in vivo* [22]. When similar strategy applied in an early phase study, manageable side effects were observed [41]. Therefore, a phase II study was performed in NSCLC patients with *KRAS* mutations who received combined selumetinib and docetaxel therapy and it showed improvement in PFS [42]. However, results of a subsequent phase III study did not show any effect of combined selumetinib and docetaxel therapy on OS, PFS, or ORR [43]. Therefore, the production of selumetinib was stopped by AstraZeneca.

A second allosteric MEK1/2 inhibitor, trametinib was also tested in a phase I trial in NSCLC patients with mutant *KRAS* and exhibited a stable disease response in 53% of patients [44]. Consequently, in a phase II trial, trametinib-treated patients had no effect on PFS. However, in three patients, 80% tumor regression was observed [45].

Cyclin Dependent Protein Kinases (CDKs) are the main regulators of cell cycle and therefore are potential therapeutic targets in NSCLC with KRAS mutations. Synthetic lethality was induced after targeting CDK in *KRAS* mutant NSCLC in *in vitro* and *in vivo* preclinical studies, suggesting that CDK plays a key role in tumorigenesis [46]. The first CDK inhibitor, flavopiridol was developed that showed little effect in phase II trials [47]. A new CDK inhibitor palbociclib has been shown to have a good effect in ER+ breast cancer patients [48]. However, its use in clinical trials for treatment of NSCLC patients is ongoing.

Another CDK inhibitor, Roscovitine was evaluated in NSCLC patients. However, it had no effect on survival [47]. Another cell cycle inhibitor, LY2835219 has been tested in xenografts and showed a good effect. A phase III trial (NCT02152631) is currently ongoing and recruiting patients.

Focal Adhesion Kinase (FAK) is another candidate to be targeted in NSCLC with *KRAS* mutation. FAK is a tyrosine kinase that is involved in cellular adhesion, invasion in different cancer types. FAK inhibition has been shown to induce tumor regression in *KRAS* mutant mice [49]. Defactinib is a FAK inhibitor that has recently been tested in Asian phase I study in Japanese patients with advanced solid tumors and showed good tolerability [50]. Defactinib has also been used in phase II trial in *KRAS* mutant NSCLC patients

(NCT01951690). However, negative unpublished results were reported at the 16th World Conference on Lung Cancer.

Conclusion

Although *KRAS* mutations are frequently observed in NSCLC patients, it is apparent that targeting mutant *KRAS* is a real challenge. The complexity of its downstream signaling pathways and the absence of oncogenic addiction made it difficult to develop an effective therapeutic approach. However, currently there are promising therapeutic trials that could effectively improve the overall survival of patients.

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