Targeting Oncogenic KRAS in Non-Small-Cell Lung Cancer

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v-Ki-ras2 Kirsten rat sarcoma viral oncogene (KRAS) is the most common driver in NSCLC, and targeting oncogenic KRAS is a major challenge in the treatment of non-small-cell lung cancer (NSCLC). The recent discovery of covalent KRAS G12C inhibitors offers hope for improving the prognosis of NSCLC patients, but the development of combination therapies corresponding to tumor characteristics is still required given the vast heterogeneity of *KRAS*-mutated NSCLC.

Keywords: v-Ki-ras2 Kirsten rat sarcoma viral oncogene ; non-small-cell lung cancer ; covalent KRAS G12C inhibitor ; combination therapy

1. Introduction

Lung cancer is the leading cause of cancer-related death worldwide. Lung cancer is classified into two major histological subtypes: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC), with the latter accounting for approximately 85% of all lung cancers. NSCLC consists mainly of lung adenocarcinomas (LUADs) and squamous cell lung carcinomas. The prognosis of lung cancer has been poor because the majority of lung cancer patients are initially diagnosed at an advanced stage. While recent developments in molecularly targeted drugs and immune checkpoint inhibitors have prolonged the survival of patients with advanced NSCLC [1][2], v-Ki-ras2 Kirsten rat sarcoma viral oncogene (*KRAS*), which is one of the most common oncogenes in NSCLC, had long been an “undruggable target” despite extensive efforts. RAS proteins are small guanosine triphosphatase (GTP)-binding proteins. The RAS family consists of three members, HRAS, NRAS and KRAS. *KRAS* knockout in mice is lethal, but *HRAS* or *NRAS* knockout mice are viable and develop normally [3][4], and KRAS can be replaced by HRAS during mouse embryogenesis [5]. Upon activation of receptor tyrosine kinases (RTKs), RAS is activated by SHP2 in cooperation with the adaptor protein GRB2 and SOS, which is a guanine nucleotide exchange factor (GEF) that catalyzes the transition of the guanosine diphosphate (GDP)-bound inactive form of RAS to the GTP-bound active form [6][7]. When *KRAS* is mutated, RAS is locked into the GTP-bound active form, which in turn constitutively activates downstream signaling pathways, such as the RAF-MEK-ERK and PI3K-AKT-mTOR pathways, conferring malignant phenotypes [8][9]. Recently, several covalent KRAS G12C inhibitors, including AMG510 (sotorasib) and MRTX849 (adagrasib), have been developed for *KRAS* G12C-mutant tumors [10][11][12]. Of note, the CodeBreaK100 clinical trial showed a beneficial effect of sotorasib in patients with advanced NSCLC harboring *KRAS* G12C mutations [13], and the FDA approved sotorasib for *KRAS* G12C-positive NSCLC patients who had received at least one prior systemic therapy in May 2021. On the other hand, KRAS G12C inhibitors do not provide as durable responses as tyrosine kinase inhibitors against EGFR or ALK; the median progression-free survival times of NSCLC patients treated with sotorasib and the EGFR-tyrosine kinase inhibitor (EGFR-TKI) osimertinib were 6.8 months [13] and 18.9 months [14], respectively. Furthermore, several secondary *KRAS* mutations and other molecular abnormalities causing resistance to covalent KRAS G12C-specific inhibitors have been reported [15][16][17]. The precise resistance mechanisms and therapeutic strategies for KRAS G12C inhibitor-resistant tumors are under investigation [18].

2. Multiple Faces of *KRAS*-Mutated NSCLC

The biological and clinical significance of *KRAS* mutations varies depending on the mutation subtype in NSCLC. For instance, G12C and G12D have higher affinities for binding to RALGDS and PI3K, respectively [19]. A recent study assessing the molecular profiles of NSCLC specimens revealed that tumors harboring *KRAS* G12C mutations exhibited a higher programmed death-ligand 1 (PD-L1) tumor proportion score and tumor mutational burden than those with *KRAS* non-G12C mutations [20]. From a clinical point of view, NSCLC patients harboring *KRAS* G12C or G12V mutations have a worse prognosis than those without these mutation subtypes [19]. In another study, surgically resected LUAD patients with *KRAS* G12C mutations had significantly shorter survival times than those with *KRAS* non-G12C mutations [21]. Therefore, targeting *KRAS* G12C seems to be an attractive therapeutic approach to improve the prognosis

of NSCLC patients. In contrast, no significant difference in the overall survival of patients with metastatic NSCLC was found among different subtypes of *KRAS* mutations [22][23]. These inconsistent observations are likely due to the intratumoral heterogeneity of *KRAS*-mutated tumors [24][25], in addition to biological and immunological differences in *KRAS* mutation subtypes [19][26].

3. Oncogenic KRAS Regulates the Tumor Microenvironment (TME)

There is growing evidence that oncogenic KRAS is involved in tumor immune evasion by regulating the TME [27]. *KRAS*-mutated NSCLC tumors have inflammatory characteristics; oncogenic KRAS induces several inflammatory cytokines and chemokines, including IL-6, IL-8, CXCL1 and CCL5, which influence the TME [28]. For instance, oncogenic KRAS mediates the secretion of IL-6, which drives protumor M2-type macrophage polarization along with the recruitment of myeloid-derived suppressor cells (MDSCs) in lung tumors [29]. Oncogenic KRAS also upregulates the expression of IL-8, a neutrophil chemoattractant, through MEK-ERK pathway activation in NSCLC cells [30]. Elevated serum IL-8 levels were found to be associated with an unfavorable prognosis in NSCLC patients treated with the PD-l antibody nivolumab, and increased IL-8 expression in tumors was negatively correlated with T cell markers and IFNγ-dependent gene signatures in the TME [31]. Another neutrophil chemoattractant, CXCL1, is also upregulated by *KRAS* mutations, and is involved in the development of lung cancer [32][33][34]. Moreover, *KRAS*-mutated NSCLC cells produce CCL5 [35], which plays an important role in antitumor immunity by promoting the recruitment of T cells and dendritic cells to the TME [36].

Several studies have demonstrated that *KRAS*-mutated NSCLC tumors exhibit PD-L1 overexpression [37], which is induced by oncogenic RAS-related pathway activation [38][39][40][41]. A previous study showed that B7-H3, T-cell immunoglobulin mucin family member 3, and indoleamine 2,3-dioxygenase-1 were highly expressed in tumor stroma-associated inflammatory cells in LUADs harboring *KRAS* mutations [42]. In addition to immune checkpoint molecules, regulatory T cells (Tregs) play a pivotal role in tumor immune evasion [43]. Mutant KRAS induces Tregs via secretion of IL-10 and transforming growth factor-β1 from tumor cells [44]. Le et al. found CD73 overexpression in *EGFR*-mutated NSCLC tumors [45]. They further demonstrated that the proportion of Tregs was decreased by coculturing these cells with conditioned medium from *EGFR*-mutated NSCLC cells with CD73 knockdown, and that an anti-CD73 antibody suppressed tumor growth in immunocompetent mice [45]. These observations suggest that *KRAS*-mutated NSCLC tumors have the ability to evade immune responses by regulating inflammatory cytokines and chemokines, immune checkpoint molecules and Tregs. Thus, targeting mutant KRAS may be an optional approach to abolish tumor immune evasion, and combination treatments including KRAS G12C inhibitors and immune checkpoint inhibitors could be effective therapeutic strategies.

4. Covalent KRAS G12C Inhibitors for *KRAS*-Mutated NSCLC

The recent discovery of covalent KRAS G12C inhibitors has changed “undruggable” oncogenic KRAS into a “druggable” target. In the KRAS G12C inactive (GDP-bound) form, the mutant cysteine residues adjacent to the switch II pocket are involved in the effector interaction [46]. The binding of covalent KRAS G12C inhibitors, such as sotorasib and adagrasib, to the switch pocket changes the nucleotide preference to favor GDP, thus impairing oncogenic KRAS-mediated signal transduction and leading to tumor regression in preclinical models [10][11].

5. Combined Therapies Involving Targeting of Oncogenic KRAS plus Other Targeted Drugs for *KRAS*-Mutated NSCLC

Oncogenic RAS upregulates downstream pathways and negatively regulates RTK signaling, whereas attenuating oncogenic RAS results in compensatory activation of RTK and wild-type RAS signaling pathways [47]. Thus, mutant RAS and wild-type RAS appear to complement each other to activate RTK-RAS signaling pathways to sustain tumor growth and survival, and the multitargeting of RAS signaling pathways could be an effective therapeutic approach. Researchers reported that the dual inhibition of KRAS and p38 inhibited tumor growth in *KRAS*-mutated colorectal cancer cells [48] and *KRAS*-mutated LUAD cells [49]. These findings suggest that blocking p38 or EGFR enhances the growth-inhibitory effect of KRAS G12C inhibitors on NSCLC tumors. In another study by Kitani et al., effective combination strategies differed between epithelial-like and mesenchymal-like *KRAS*-mutant NSCLC cells; a combination therapy with the MEK inhibitor trametinib plus the EGFR-TKI afatinib was effective for epithelial-like tumors, while the dual blockade of MEK and FGFR effectively suppressed mesenchymal tumor growth [50]. A recent study demonstrated that combined treatment with the KRAS G12C inhibitor ARS-1620 plus the pan-PI3K inhibitor GDC0941 consistently suppressed tumor growth in ARS-1620-resistant *KRAS*-mutated tumors, whereas the growth-inhibitory effects of ARS-1620 plus afatinib or cetuximab varied among *KRAS*-mutated cell lines [51]. Together, these observations indicate that the therapeutic efficacy of covalent KRAS G12C inhibitors varies depending on the biological properties of the treated *KRAS*-mutated tumors.

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