EDITORIAL

KRAS Association with Lung Cancer: An Overview

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Journal of Medical Academics (2021): 10.5005/jp-journals-11003-0110

The chief cause of cancer-related deaths is lung cancer. Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation has been documented to be the most frequent mutation in lung cancers. The rat sarcoma virus (RAS) family includes KRAS, Harvey rat sarcoma virus, and neuroblastoma RAS viral oncogene homolog. All RAS family oncogene mutations have been observed in lung cancer.[1,2] Lung adenocarcinoma is the most common presentation of non-small cell lung cancer (NSCLC).

Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations are most frequent in lung adenocarcinoma[3,4] but less frequent in squamous cell carcinoma.[5] KRAS is most frequently mutated at codon 12 and less frequently at codon 13 and codon 61. The presence of KRAS mutations decreases the response to epidermal growth factor receptor (EGFR) inhibitors in NSCLC.[3]

The three RAS genes are highly conserved and encode the guanine nucleotide-binding proteins (GTPases) that cycle between active and inactive states in response to extracellular cubes.[1] KRAS undergoes alternate splicing, which results in the formation of two proteins—KRAS4A and KRAS4B. KRAS4A protein and KRAS4B differ only at their carboxyl termini.[1,5] KRAS4B is developmentally essential with unique functions that other RAS members cannot compensate. The specific type of KRAS mutations may be helpful in providing information with respect to disease aggressiveness and drug sensitivity. There is ample data with respect to the usefulness of KRAS status as a marker for therapeutic response. This review article aims to study the mutations of KRAS and its associated genes in different types of lung cancer and the signaling pathways involved in the pathogenesis of these mutations.[1,3,4]

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How to cite this article: Rustagi P, Rustagi SM. KRAS Association with Lung Cancer: An Overview. J Med Acad 2021;4(2):33–35.

Source of support: Nil

Conflict of interest: None

Introduction

Rat sarcoma virus (RAS) proteins are GTPases that stimulate many pathways in cellular growth. In NSCLC diagnosed cases, approximately, 25–35% of individuals exhibit V-Ki-RAS2 KRAS mutations.[5] Of these KRAS mutations, the single point mutations diagnosed 40% in glycine-to-cysteine substitution at codon 12 (G12C), 21% in glycine-to-valine substitution at codon 12, 17% in glycine-to-aspartate substitution at codon 12 (G12D), 10% in glycine-to-alanine substitution at codon 12, and 12% in other G12 and G13 mutations. Around 25–35% of patients with a smoking history show KRAS mutations. Smokers exhibit more G > T transversion mutation. KRAS mutation leads to impaired GTPase activity and higher levels of pro-oncogenic compound GTP-KRAS in the cytoplasm. KRAS encodes GTPase membrane-bound protein whose GTP-bound active form transduces signals which activate fundamental signaling pathways in the cell.[4–6]

Rat sarcoma virus (RAS) activation is controlled by guanine nucleotide exchange factors (GEFs) and GTPase activating proteins (GAPs). GEFs cause an increase in the concentration of guanosine diphosphate (GDP) by release from RAS and exchanging it with GTP. Thus, RAS gets activated. The intrinsic GTPase activity of RAS is increased by GAPs and converts RAS from an active to an inactive form. The mutated RAS oncoprotein prevents GAP from enhancing the catalytic activity of GTPase and keeps it in an activated state, which activates oncogenic pathways. The mitogen activated protein kinase pathway (MAPK) pathway begins with the kinase RAS. RAS phosphorylates mitogen-activated protein kinase kinase (MEK) and subsequently activates extracellular signal-regulated kinase (ERK). The MAPK pathway incorporates four kinases-MAPK, MAPKK, MAPK 3K, and MAPK 4K, which activate and phosphorylate downstream proteins. MAPK pathway is the central signaling component that controls cell proliferation and differentiation. This pathway transfers signals through step-wise activation of 3–5 layers of protein kinases named MAPK kinase kinase kinase (MAP4K), MAPK kinase kinase (MAP3K), MAPK kinase (MAPKK), MAPK, and MAPK-activated protein kinases (MAPKAPK).

Malfunctioning of the Ras-ERK pathway is a major activator for most cancers. ERK stimulates cytosolic substrates and relocates to the nucleus for the expression of genes involved in cell proliferation, differentiation and cell cycle regulation.[3,4]

Point Mutations in NSCLC and their Effects

Carcinogenic KRAS is the most common mutation in NSCLC, which accounts for approximately one-third of lung adenocarcinomas in the west and one-tenth of patients in Asian countries. Patients having lung cancer due to KRAS mutations show these mutations most commonly at codon 12 (G12) along with some amounts of mutations at codons 13 and 61.[4–6] KRAS remains active in the GTP bound state and becomes inactive in the GDP bound state; these states are in turn controlled by GEFs and GAPs. Carcinogenic mutations in KRAS result in impairment of the ability to hydrolyze GTP, which results in engagement of gene in an active state of KRAS downstream signaling.[3,4] This results in uncontrolled cell proliferation. KRAS mutations are infrequent in squamous cell carcinoma and mostly occur in adenocarcinomas. Point mutations in KRAS affect the codon 12 of the protein, which leads to amino

acid substitutions that render the KRAS oncoprotein active. Molecular modeling of KRAS oncogene substitutions shows that these mutations lead to downstream signaling of transducers.[4,6]

The different amino acid substitutions of KRAS mutation show different clinical outcomes. KRAS G12C shows higher ERK phosphorylation and are more amenable to MEK inhibitor than KRAS G12D. This has helped in increasing chemotherapeutic efficiency. Oncogenic KRAS activates various downstream pathways, which are characterized by phosphatidylinositol 3-kinase (PI3K) and MAPK. These downstream affecters lead to phenotypic variants in cancer. There are two identified types of KRAS mutant cancers that are dependent on ribosomal protein S6 kinase A1. These two subtypes differ in metabolic status and have different vulnerabilities.[4]

Treatment of KRAS Mutant Lung Cancer

Kirsten rat sarcoma viral oncogene homolog mutations activate different downstream signaling pathways and increase activation of the MAPK pathway. The most frequently occurring mutation of KRAS, that is, G12C substitution, shows more engagement with MAPK signaling; thus, the drug that uses MEK inhibitors is more applicable to this mutation.

Kirsten rat sarcoma viral oncogene homolog was considered to be undruggable as a clear binding pocket was not identified. Small molecules that recognize and irreversibly deactivate specific KRAS mutant alleles with a G12C amino acid substitution using modern screening technology called tethering. ARS-853, the drug was developed to selectively reduce KRAS-GTP levels by >10% and increase the hydrolytic reaction rate by 600 times. ARS 853 also suppressed MAPK and PI3K-protein kinase B signaling.[4,5]

Adagrasib (KRASG12C inhibitor) (MRTX 849) is a very strong, highly selective small molecule inhibitor of KRAS-G12C. MRTX 849 shows broad-spectrum anti-cancer activity.[3,4] Other blocking drugs that inhibit mutant KRAS include AZD 4785, which has a KRAS antisense oligonucleotide, but it is not used due to its effect on both mutant and non-mutant KRAS mRNA.[5,6]

As KRAS shows a preference for hyperactivation of MAPK, a pooled drug sensitivity analysis was conducted, which gave the result that MEK inhibitors are more sensitive to KRAS mutant cancer as compared to other pathway inhibitors. Only targeting the MAPK pathway results in the development of resistance which can involve activation of various other oncogenic pathways. Thus, inhibition of SRC homology region 2 containing protein tyrosine phosphatase. SRC oncoprotein has two small protein binding domains, one of them is the SRC domain. SHP2 is involved in the transmission of signals downstream of several RTKs and has been associated with several types of cancers. SRC homology tyrosine phosphatase region 2 (SHP2) is essential for the complete activation of the MAPK pathway. The suppression of SHP2 activity would block RAS/MAPK signaling and, in turn, stop tumor cell survival and proliferation that it promotes.

SRC homology tyrosine phosphatase region 2 (SHP2) rewiring was required to reestablish MEPK signaling. SHP2 is encoded by the PTPN11 gene. Strong synergy between SHP2 rewiring and MEK inhibitors simultaneously targeting mutant KRAS growth in different models.[3,4]

Rewiring KRAS Activation

Kirsten rat sarcoma viral oncogene homolog (KRAS) becomes active in response to upstream receptor tyrosine kinases, but mutated KRAS is in a perpetually active state. KRAS mutant cancers generally show a poor response to EGFR inhibitors. However, recent studies have shown that activation of epidermal growth factor receptor (receptor protein kinases) (ERBB) signaling was required for lung cancer driven by KRAS G12D mutation. ERBB inhibition was very effective in controlling KRAS mutant tumor growth.[2,7,8] Neratinib, a drug responsible for multi ERBB inhibition, almost stopped the emergence of KRAS mutant tumor.[4,5] However, EGFR inhibition leads to tumor escape mechanism wherein other EGFR mechanisms are utilized for resistance.[5] The increased ERBB activity leads to the establishment of a feed-forward loop that amplifies signaling through the core RAS-ERK pathway. This leads to survival and proliferation in KRAS-mutant NSCLC. Complete ERBB inhibition increased the potency of MEK inhibition *in vitro* and *in vivo*.

ERBB signaling supports the progression of KRASG12D-driven lung cancer. An independent pan-ERBB inhibitor, Afatinib, was used, which showed that EGFR deletion attenuates mutant KRAS activity and transiently reduces tumor growth.[8]

Revitalizing Chemotherapy

In recent times, platinum-based chemotherapy has been the gold standard used for the treatment of KRAS mutant lung cancer. But the period of response is brief, and the effect is limited. A recent phase III study showed no additional survival benefit in platinum-based chemotherapy.[9] Activation of mammalian target of rapamycin (mTOR) signaling is the chief resistance mechanism to chemotherapy which is observed in a hyper-activated state in KRAS mutated lung cancer.[10] mTOR inhibitor along with chemotherapy shows strong inhibiting proficiency of mutant cells.[1] The combination of platinum-based chemotherapy with mTOR inhibitor treatment correlates with the magnitude of mTOR activity caused by chemotherapy alone.

Recent research reported that pemetrexed-resistant KRAS-mutant lung cancer cells modify to a mesenchymal phenotype and cross-resist MEK inhibitors.[8] As KRAS-mutant lung cancer cells acquire resistance, they bypass canonical KRAS effectors but cause hyperactive AXL/eukaryotic translation initiation factor 4E, increased protein turnover in the endoplasmic reticulum (ER), and adaptive activation of an ER stress-relief unfolded protein response survival pathway whose integrity is maintained by HSP90.[8] HSP90 inhibitor NVP-AUY922 inhibited NSCLC tumor cells and made the tumor stable.[11] In line with these findings, HSP90 inhibitors synergistically enhance the antitumor effects of pemetrexed and MEK inhibitors in multiple *in vitro* and *in vivo* models, validating a rational combination strategy to treat KRAS-mutant lung cancer.

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