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Mini Review

The Mutations of KRAS Gene in Lung Cancer: Real Targets or Epiphenomenon?

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Abstract

Background: The most described oncogenes in lung cancer are those encoding for EGFR (epidermal growth factor receptor) and KRAS. The mutations of the gene KRAS have been described since two decades. In spite of that fact, the assessment of their implication in lung cancer remains debated.

Aim: We aim to assess the real impact of the mutations of KRAS on the prognosis and treatment of non-small cell lung cancer through a mini review of the literature.

Methods: We performed a mini-review of the literature through the pubmed site using the key-words: KRAS gene, KRAS mutations in lung cancer.

Results: Through this review of the literature, we noticed the multiplicity of the studies dealing with this subject and the absence of consensus concerning the consequences of these mutations on the management of the patients.

Conclusion: KRAS mutations play a key role in the carcinogenesis of lung cancer. In the presence of mutations, this way becomes autonomous and interacts with other ways mainly PI3K and MEK. A better knowledge of these mutations will enable a prediction of the answer to anti-EGFR therapy. Besides, other therapeutic targets will be explored in non responders' patients.

Keywords: KRAS gene; Target therapies; EGFR gene; Sequencing

Introduction

Lung cancer is the first death related cause by cancer in the world. Two major groups are individualized represented by small cell carcinomas and non-small cell carcinomas. The latter are the most frequent and represent an example of genetic disease secondary to genomic alterations. The most frequently described oncogenes are EGFR (epidermal growth factor receptor) and KRAS. In spite of the discovery of KRAS mutations since about two decades and the assessment of their implications in many cancers such as colorectal cancer, grelic cancer, pancreatic cancer or biliary cancer, this pathway remains under-explored in comparison with EGFR pathway [1]. Recent studies about patients with non-small cell lung carcinoma that were non responders to EGFR inhibitors put emphasis on the consequences of KRAS mutations on the response to the treatment.

Particularity of k-ras gene

Ras family involves the genes K-ras, v-Ha-ras (Harvey rat sarcoma viral oncogene) and the oncogene viral N-ras viral (neuroblastoma RAS viral oncogene). These genes encode for a guanine triphosphate binding protein family inducing cell proliferation, differentiation and apoptosis and interacting with MAPK (mitogen-activated protein kinase) and STAT (signal transducer and activator of transcription and PI3K (phospho-inositide-3 kinase) pathways [2]. In non-small cell lung carcinomas, 90% of the mutations are localized in the KRAS gene.

Mutations of k-ras

About 15% to 25% of the patients with non-small cell carcinomas present mutations of KRAS gene. The exons 1 and 2 are affected in 97% of the cases (G12, G13 and Q61) [3]. These mutations affect the intrinsic activity of the GTPase and induce a resistance to the GTPases activators. Enhancing mutations of KRAS induce the stimulation of PI3K and MAPK pathways.

Means of diagnosis of kras mutations

Many diagnostic methods exist including the direct sequencing, the pyrosequencing, the DHPLC, the HRM (high resolution melting), the real time PCR…. New diagnostic techniques include ARMS, the SNaPshot and the next generation sequencing. All these methods present advantages and disadvantages in terms of cost, sensitivity and delay of response [4,5]. The direct sequencing represents the gold standard method for the diagnosis of KRAS mutations in routine despite its low sensitivity estimated to 20%. The HRM technique has a sensitivity of 5% but seems to be difficult in routine. Real time PCR is a sensitive technique with a sensitivity of 1-2%. Tuonenen and coworkers compared the DNA arrays to the real time PCR in the detection of EGFR, KRAS and BRAF mutations. They reported a good concordance between both techniques [6]. Recently, the SNaPshot technique has been reported to be sensitive necessitating only 10% of tumor cells. A bioship essay has also been reported about the detection of the KRAS mutations with a sensitivity of 10% but this technique seems to be difficult to perform routinely [5]. Pyro-sequencing technique uses 4 enzymes (DNA polymerase, ATP sulfurylase, luciferase and apyrase) and 2 substrates (Adenosine 5´ PhosphoSulfate (APS) and luciferine). Pyro-sequencing is a quantitative method used routinely with a sensitivity of 5%.

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Mutations of kras and smoking

In opposition to the EGFR mutations, KRAS mutations are more frequent in Caucasians with a frequency of 25 to 50% [7,8] and are more frequently observed in smokers [2,9,10].

Mutations of kras gene and histologic subtype

KRAS mutations are more frequently described in adenocarcinomas (30%) and are less frequent in squamous cell carcinomas (approximately 5%) [11].

Prognostic impact of kras mutations

The prognostic impact of KRAS mutations remains debated and nonconsensual. Graziano et al. or Keohavong et al. and Lu et al. reported no prognostic correlation with KRAS mutations [12-14]. These authors studies the survival of the patients presented localized lung cancers (stage I or II). Slebos and coworkers reported a 69-patient-study and concluded that the mutations of the codon 12 were predictive of a poor prognosis [15]. In a Japanese study, the authors reported that patients with KRAS wild-type tumors had a better prognosis than those with KRAS mutations [16,17]. In a prospective study about 365 patients with localized lung cancers, the authors demonstrated that KRAS mutations were observed only in smokers and had prognostic implications in patients with adenocarcinomas [18]. In 2005, a review of the literature with meta-analysis of 28 series including 3620 patients, demonstrated that the presence of KRAS mutations was correlated to a poor prognosis in patients with adenocarcinomas [19].

Kras mutations and response to egfr inhibitors

The activation of EGFR pathway induces a cascade phosphorylation of the viral oncogene RAS (rat sarcoma viral oncogene), RAF (v-raf murine leukemia viral oncogene homolog), MEK (murine thymoma viral oncogene homolog), ERK (extra cellular-signal-regulated kinase), PI3K/AKT (phosphatidylinositol 3-kinase). These interactions induce cell proliferation, neo-angiogenesis and metastatic potential of tumor cells [20]. The inhibition of the EGFR kinase activity induces a response in 75% of the patients with EGFR mutations and in 10% of the patients with EGFR wild type tumors [21]. In opposition to colorectal cancer, the impact of the KRAS mutations of the response to EGFR inhibitors isn't consensual. In a meta-analysis about 1335 patients treated with gefitinib or erlotinib, the mutations of KRAS were correlated to a poor response to the EGFR inhibitors [8]. The KRAS mutations were detected in 16% of the patients mainly with adenocarcinoma. Patients with KRAS mutations presented less sensitivity to EGFR inhibitors with a relative risk of 3% versus 26%.

Perspectives of targeting kras

In spite of the multiplicity of therapeutic essays using anti-KRAS drugs, results remain disappointing. The best management of the patients with KRAS mutations seems related to the association of KRAS inhibitors to other specific therapeutic agents. These pathways may represent therapeutic targets in association to KRAS targets.

- PI3K and MEK pathways

These pathways represent promising therapeutic targets in patients with PI3K mutations combined to an inhibition of MEK. Engelman et al. treated mouses with non small cell lung carcinoma with KRAS mutations with inhibitors of PI3K and MEK. This association induced a decrease of the tumor volume [22]. Janne et al. reported a study about patients with advanced KRAS mutated non small cell lung carcinoma treated with MEK inhibitors. They reported a good clinical response [23].

- Serine threonine kinase 11 (STK11) pathway

LKB1/ serine threonine kinase 11 is inactivated in 30% of the non small cell lung carcinomas. Loss of homozygote of this gene associated to KRAS mutations seems to be correlated to aggressiveness [24,25].

- NF1 pathway

The loss of NF1 induces RAS hyperactivity in non small cell lung carcinomas. Inhibiting mutation of NF1 is exclusively associated to KRAS mutations and activation in 40% of the cases.

- WT1 pathway

The gene of the Wilms tumor seems to play a regulating role on KRAS. Vincent et al. identified a new role of WT gene. The loss of the WT1 oncogene seems to be associated to a death process in KRAS expressing cells [26]. These results may encourage targeting WT1.

- Other signaling pathways have also been reported as potential therapeutic targets including NK-KB, activators of Zeste Homolog 2, GATA-binding factor 2, RNA-binding Motif 5, Il8, Twist-related protein 1[27].

Conclusion

KRAS pathway plays an important role in the carcinogenesis of non small cell lung carcinomas. In case of mutation, this pathway which is normally activated by EGFR becomes autonomous and acts with other pathways mainly PI3K and MEK. The improvement of the knowledge about the KRAS mutations induced the discovery of mutations predictive of poor response to EGFR inhibitors. Besides, many authors reported the necessity of inhibiting many targets in non-responders patients to EGFR. This fact highlights the future role of targeting the KRAS pathway.

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