



# CLINICAL SIGNIFICANCE OF THE KRAS MUTATION

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## ABSTRACT

The challenge of translational medicine is to translate very complex scientific data into the clinical setting so that medical management can be better guided towards the ultimate goal of better patient outcome. Physicians now have the opportunity to use specific biomarkers to personalize therapeutic options in various settings. Recent research has demonstrated that presence of Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation may directly influence medical decisions in patients with colon and lung cancer.

Use of KRAS oncogene as a selection marker for specific treatment is a good example of individualized medicine approach to cancer treatment

KEY WORDS: KRAS mutation, prognostic biomarker, selection marker

## INTRODUCTION

One KRAS (Kirsten rat sarcoma viral oncogene homolog) mutation is present in up to 25% of all human tumors, and this is one of the most frequently activated oncogenes(1). Recent research has demonstrated that presence of KRAS mutation may directly influence medical decisions in patients with colon and lung cancer. This review article will briefly discuss the following concepts about Kras oncogene that may be significant for practicing physicians:

1. RAS oncogene and Carcinogenesis as a multistep process
2. KRAS MUTATION AS A PROGNOSTIC BIOMARKER IN NON SMALL CELL LUNG CANCER
3. KRAS as a selection marker for EGFR inhibitor treatment in colon cancer.
4. KRAS mutation and resistance to erlotinib
5. KRAS mutation and response to bevacizumab
6. KRAS mutation and Personalized Medicine

*KRAS oncogene and Carcinogenesis as a multistep process*

Alterations in oncogenes, tumor-suppressor genes, and micro-RNA genes are important in pathogenesis of cancer (2). These alterations are a sequential multistep process that in the end results in neoplastic transformation. The accumulation of multiple genetic mutations occurs over significant period of time. For example, time required for transformation of colon adenoma to colon carcinoma may be up to 10 years. Generally for this process mutational activation of oncogenes and the inactivation of tumor suppressor genes are both necessary (3). Somatic mutations in at least four or five genes of a cell are crucial for a malignant transformation. Oncogenes are normal genes with an important role in the process of stimulation of controlled cellular proliferation. Mutations in these genes result in uncontrolled proliferation and development of cancer. RAS genes are expressed in normal cells, and are involved in controlled cell growth. Three distinct mutations of RAS have been identified: H-ras, N-ras, and K-ras. In general, colon, pancreas and lung carcinomas have mutations of KRAS, bladder tumors have HRAS mutations, and hematopoietic neoplasms are associated with NRAS mutations. RAS mutations are infrequent in breast cancer. It is important to emphasize that activation of RAS oncogene is only one component in the 'genetic cascade' of events that finally results in malignant transformation (4). Given the development of cancer is a multistage process theoretically it is not likely that understanding the role of one mutation will have a direct impact on therapeutic decision. However, recent research showed that analysis of a single mutation may have a direct influence on a treatment selection.

*KRAS mutation as a prognostic biomarker in non-small cell lung cancer*

KRAS mutation in a non-small cell lung cancer is associated with smoking. Lung cancers with K-ras point mutations have worse prognosis and a tendency to be smaller and less differentiated than those without mutations. (5) In one study 63% of patients with K-ras mutation and completely resected adenocarcinoma of the lung died during the follow-up period as compared with 32% of patients with no mutation in the K-ras oncogene ( $P = 0.002$ ) (5). The protein product of the Ras oncogene is called p21. Immunohistochemical staining on paraffin sec-

tions using anti-ras p21 monoclonal antibody can detect p21 ras protein and can be used as a prognostic test. In a study of 116 surgically treated patients with non-small cell lung cancer, overexpression of p21 ras protein was associated with a poor prognosis. Patients with strongly positive reactions (++) had a 5-year survival rate of only 11.5%. In contrast, patients with p21-negative tumors had significantly longer survival times (a 5-year survival rate of 64.1%) (6). The correlation between p21 staining and patient survival in this study was independent of stage of disease, node status, histologic type, and the resectability of tumors. Although Ras mutations are associated with adenocarcinoma of the lung, these mutations may also be present in patients with squamous cell carcinoma of the lung.

*KRAS as a selection marker for EGFR inhibitor treatment in colon cancer*

KRAS can serve as a selection marker for EGFR inhibitor treatment in colon cancer (7). KRAS mutations can be identified using polymerase chain reaction on DNA from tumor tissue. KRAS mutations are detected in approximately 30% to 50% of patients with colorectal cancer. Panitumumab, a fully human antibody against the epidermal growth factor receptor (EGFR), is an effective monotherapy option for patients with relapsed or refractory EGFR-expressing metastatic colon cancer. There is evidence that the presence of KRAS mutation in lung and colon cancers is associated with lack of response to EGFR inhibitors (7). There is no clinical benefit to panitumumab therapy in colon cancer patients with KRAS mutation since the inhibition of the RAS/RAF/MAPK signaling pathway is important for the activity of panitumumab in metastatic colorectal cancer. In a study of 427 patients, metastatic colorectal cancer KRAS mutations were found in 43% of patients. This group of patients had no response to panitumumab treatment (response rate 0%) This is an example of how information about only one oncogene mutation can directly influence a treatment decision. It is obvious that KRAS status should be analyzed before the administration of panitumumab in patients with metastatic colorectal cancer. Patients with KRAS mutation demonstrated no benefit from treatment with another EGFR inhibitor, cetuximab. In the study from the L'Institut National de la Santé et de la Recherche Médicale, none of the patients with colorectal carcinoma who had a KRAS mutation had a response to cetuximab (8). In the same

study skin toxicity was not sufficient to predict outcome in patients treated with cetuximab and KRAS mutation status provided supplementary information. EGFR expression based on Immunohistochemistry (IHC) is not clinically useful to predict response to cetuximab. There is a large number of growth factor-dependent and -independent mechanisms for activating the EGF receptor and it can be activated by receptor over-expression as in the case in colorectal cancer. Monoclonal antibodies that bind and block EGFR signaling may be important in therapy of metastatic colorectal cancer. However, mutations of the K-RAS protein result in increased cancer proliferation and metastasis even in the presence of EGFR inhibition. Cetuximab or panitumumab are active in wild-type *KRAS* colorectal cancers. These monoclonal antibodies inhibit binding of the ligands of EGF (epidermal growth factor) and TGF alpha (transforming growth factor) to EGFR. Therefore, signaling of the RAS pathway is inhibited. Therefore Cetuximab or panitumumab are effective and should be used in colon cancer patients with wild-type *KRAS*. In contrast, K-RAS mutation promotes downstream signaling in the presence of EGFR inhibition. This process will stimulate cancer proliferation, angiogenesis and metastasis. Consequently mutations of the K-RAS protein result in increased cancer progression even in the presence of EGFR inhibition. In this clinical situation, if K-RAS mutation is present in patients with colon cancer, oncologist should not use Cetuximab or panitumumab. This is a good example of personalized or individualized medicine.

#### *KRAS mutation and resistance to erlotinib*

EGFR and *KRAS* mutations are considered to be mutually exclusive (9).

Non-Small Lung Cancer patients with *KRAS* mutations have primary resistance to erlotinib (9). Again this may be an example of a individualized treatment decision on the basis of biomarkers. Patients with an EGFR mutation but not a *KRAS* mutation have a high probability of response to erlotinib. Those tumor cells that are positive for a *KRAS* mutation and negative for the EGFR mutation are resistant to erlotinib; thus, this costly treatment in this group of patient should be not used.

#### *KRAS mutation and response to bevacizumab*

Can *KRAS* mutation predict response to bevacizumab? In a study of 230 patients treated with irinotecan, fluoro-

uracil, and leucovorin (IFL) in combination with either bevacizumab or placebo *K-ras* status was assessed (10). The median progression-free survival (PFS) in patients with wild-type of *KRAS* was 13.5 months for group treated with irinotecan, fluorouracil, leucovorin and bevacizumab (IFLB) versus 7.4 months for the group treated with irinotecan, fluorouracil, leucovorin and placebo (IFLP) (hazard ratio 0.44,  $p < .0001$ ). Metastatic colon cancer patients with *KRAS* mutations treated with irinotecan, fluorouracil, leucovorin and bevacizumab (IFLB) had progression-free survival (PFS) of 9.3 months versus 5.5 months (hazard ratio 0.41,  $p = 0.0008$ ) for the group treated with irinotecan, fluorouracil, and leucovorin without bevacizumab. Despite of the fact that patients with *KRAS* mutations had inferior progression-free survival (PFS) than patients with wild-type of *KRAS*, addition of bevacizumab to IFL still provided a significant clinical benefit to the *KRAS* mutations group. This suggests that action of bevacizumab may be independent of alterations in the Ras/Raf/Mek/Erk pathway (10).

#### *KRAS mutation and Personalized Medicine*

The challenge of clinical medicine is to translate very complex scientific data into the clinical setting so that medical management can be better guided (11). Therefore, a concept of personalized medicine becomes very important in clinical oncology. Our general goal is to individualize treatment depending on both cancer and patient characteristics. This personalized or tailored therapy may improve outcomes (12). Physicians now have the opportunity to use biomarkers to personalize therapeutic options. For example, for patients with metastatic colorectal cancer who have progressed after cytotoxic therapy, the goal of treatment is to stabilize disease with minimal toxicity. Thus, one can select patients with a wild-type *KRAS* tumor and treat them with Cetuximab or panitumumab. In contrast, there is no benefit of Cetuximab or panitumumab therapy in colon cancer with *KRAS* mutation and this costly treatment should not be used in this group of patients. *KRAS* mutation in non-small Lung Cancer is also associated with resistance to erlotinib. Hence, a physician should not use this very expensive drug in the treatment of Non Small Lung Cancer with a *KRAS* mutation.

## CONCLUSION

KRAS mutation is selection biomarker that can directly influence medical decision making in patients with colon cancer. Clinical use of information provided by testing for KRAS mutation may serve as a example of personalized medicine.

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