Commentary

KRAS mutations: efficacy and sensitivity of early predictive screening of cancer progression require other gene mutations in addition to KRAS

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The *KRAS* gene, also known as Kristen rat sarcoma viral oncogene homolog, is a member of the Ras family of cell proliferation regulators and plays an important role in cancer progression upon the mutation induced activation of this gene (1). A significant role that they play is in a cell proliferation signaling cascade that involves receptor to nucleus signal transduction and therefore the activation of this pathway is under tight control (1,2). In normal cells, the Ras proteins exist in two forms: the active form, when the protein is bound to GTP and the inactive form when they are bound to GDP (1). The action of this signaling cascade is under the control of an enzyme located on the Ras protein, a GTPase, which cleaves the GTP molecule from the Ras protein and effectively prevents signal transduction to the nucleus by transforming it into the inactive GDP-bound Ras and halts the growth signals (2). The ratio between the inactive and active forms of the Ras protein maintain cell growth and proliferation in normal cells. The mutation that occurs is the result of a point mutation at position 12, 13 or 61 of the gene that codes for GTPase activity (1). The mutation on codon 12, which is particularly prevalent in pancreatic cancers, substitutes glycine for a valine or aspartate (3) and leads to GTPase losing its function and essentially allows GTP to continue to signal cell growth (4), thereby allowing uncontrolled and continuous growth, angiogenesis as well as overriding apoptosis (1,2). It has been well documented that a mutation in this gene leads to a number of malignancies including lung (5), colorectal (3,6) and pancreatic (7). Many groups have opted to use a mutation in this gene as a biomarker for the malignancies listed, especially pancreatic cancer as it is one of the most difficult cancers to detect and is more often than not detected late in its development (8).

A recent publication by Le Calvez-Kelm *et al*. (9) has proposed that KRAS mutations circulation in plasma in the form of cell-free DNA could potentially be used as an early diagnostic method for individuals exhibiting symptoms of pancreatic cancer and to possibly detect the development of pancreatic cancer in asymptomatic individuals. Their method of detection involved deep sequencing of KRAS codons 12, 13, and 61 [where the mutations have been documented to occur (7)] of plasma samples from 400 pancreatic cancer patients and 500 controls. Much of this study confirmed findings of other groups that suggested the use of KRAS as a diagnostic tool for early pancreatic cancer detection. However, while many studies have been conducted on the KRAS mutation and its efficacy as a diagnostic tool (7,10,11), as stated by the authors, such a large case-control study on the KRAS mutation has not been done using the sequencing techniques described by this study. While the authors should be commended on their efforts to elucidate a more accurate diagnostic method to detect pancreatic cancer, their method was not as sensitive as the authors anticipated and offered a plausible

explanation for this reduced sensitivity, that being the biology of pancreatic malignancies.

In addition to this being a reason for the reduced sensitivity to detection of pancreatic cancer, one might also consider the efficacy of screening for additional mutations that work in conjunction with KRAS to increase sensitivity of detection. For example, a small scale study conducted by Pellegata *et al*. (12), showed that KRAS and p53 mutations interacted with each other to establish ductal pancreatic cancer, one of the most common pancreatic tumor studied. Mutations in both KRAS and p53 were identified to have taken place in pancreatic cell lines and are suggested to lead to a malignant phenotype (12). Their ultimate finding was that a KRAS and a p53 mutation cannot be used to identify nonductal exocrine or endocrine tumors of the pancreas and this was due to the cell type that was present in other nonductal compartments of the pancreas. Therefore, the biology of the pancreatic malignancy is a likely explanation for the reduced sensitivity in detecting pancreatic cancers. Lung carcinoma studies have suggested a similar cooperation between the KRAS mutation and EGFR mutation in relation to decreased therapeutic potential of EGFR tyrosine kinase inhibitor therapy (5) and have suggested using the presence of both these mutations as predictors of resistance to traditional treatments that target the EGFR on lung cancers. Using these findings as a guide, another avenue that could be explored is the possibility of the interaction of the KRAS mutation in conjunction with other mutations that are also hallmarks of nonductal pancreatic cancers in order to cover a broader scope of pancreatic cancers and possibly increase sensitivity and develop better early detection methods.

Furthermore, in relation to reduced sensitivity of the KRAS mutation as a diagnostic tool, other groups have encountered similar hurdles with respect to using this gene mutation to detect pancreatic cancer because of the overlap between this gene being expressed by pancreatic patients as well as individuals exhibiting pancreatitis (8). While Le Calvez-Kelm took this into consideration and used blood serum samples from patients with pancreatitis as a control group, their findings only acted to confirm what other groups have found when using this mutation as a detection method.

Lastly, the presence of KRAS has also been used as a predictor for resistance to EGFR inhibitor therapies (13) and cancer aggressiveness (6), particularly in colorectal cancers and has been recently applied to lung cancers as well (5). Such predictive methods allow for a treatment strategy to be developed that is both cost effective and possibly more promising allowing patients to have a better chance of survival. As such, one group has suggested that using KRAS in a similar fashion as a predictive tool in relation to tumor burden and tailoring therapies accordingly would be far more efficacious than using this mutation as an early detection tool for pancreatic cancer (14). Furthermore, other studies have shown that the presence of KRAS is a better predictor of a poor prognosis rather than an early detection method (15).

In conclusion, the KRAS mutation has been thoroughly studied with regard to its relationship with cancer progression in a number of cancer types; however, its efficacy as an early detector of pancreatic cancer has yet to show promise as its presence seems to be a far more accurate predictor of poor prognosis. Therefore, one avenue that could be explored, as it has not been thoroughly researched in the literature, is as a predictor of which treatment options might be more successful as it has been done in colorectal and lung cancers. An alternative avenue would be to determine if additional mutations could be screened in addition to KRAS in the blood plasma as an early detection method.

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Footnote

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