Review of: "RAS mutations that have a major impact on current cancer genomic medicine"

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In this Communication Letter “RAS mutations that have a major impact on current cancer genomic medicine” Hayashi et al. focus on how splicing mutations of RAS lead to unfunctional protein.

Alternative splicing changes are frequently observed in cancer and are starting to be recognized as important signatures for tumor progression and therapy. It has been already shown that a subset of alternative splicing changes affect protein domain families that are frequently mutated in tumors and potentially disrupt protein-protein interactions in cancer-related pathways.

However, their functional impact and relevance to tumorigenesis remain mostly unknown.

The authors specifically focus on RAS family genes (which are found in up to 20% of cancers) and in particular on colorectal cancer.

Data from the phase III FLAURA study, showed that acquired somatic mutations in *KRAS* (G12C, G12D, Q61K and A146T) drive resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor osimertinib in *EGFR*-mutant lung cancers, warranting the development of alternative Q61X-selective therapeutic strategies.

Kobayashi et al., showed that the allele frequencies of two other *KRASQ61K* alleles, both containing a concurrent silent mutation at G60, GQ60GK (c.180_181delinsCA or AA), increased sharply in response to osimertinib treatment, while cells harboring *KRASQ61K* without this silent mutation did not impart resistance.

Mechanistically, it was shown that the mutation resulting in KRAS(Q61K) (c.181C>A) simultaneously introduces a putative cryptic splice donor site at that location, with a consensus value equivalent to the canonical splice donor site between exon 3 and intron 3 resulting in an aberrant splicing event producing the non-functional Q61K variant.

Based on these and other data, the authors tested 318 patients with recurrent colon cancer for RAS Q61K mutations and detected the variants in 5 patients (so designing them at first as “oncogenic’). However, taking into consideration Kobayashi article, the authors proved that these are rather nonfunctional KRAS proteins caused by altered splicing from the cryptic splice donor site.

Comments

All in all, this is a very nice example of how personalized medical care represents the future of cancer treatment and medicine, especially in the field of drug resistance.

Points to be addressed:

- It would be advisable to give some more background about KRAS(Q61) mutants and the silent mutation at G60, GQ60GK (c.180_181delinsCA or AA),
- The authors claim that KRAS were not-functional variants basing on DNA/RNA gene sequence analysis. Did the authors look at the protein product and effects on downstream signaling too? For instance, by looking at the expression of ERK signature genes
- The authors mentioned panitumumab as anti-EGFR inhibitor. First, they should give some more details about it (i.e. where it binds, etc). Secondly, this is monoclonal antibody, while Kobayashi et al. used osimertinib (an irreversible TKI inhibitor) to inhibit EGFR.