Researchers make progress on early detection of resistance to colorectal cancer drugs

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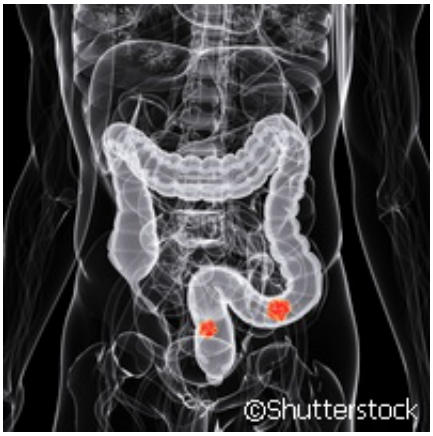

Mutations in a gene called KRAS are causally associated with acquired resistance to targeted therapies for colorectal cancers (CRC), according to new findings from EU-funded researchers from Italy and their research colleagues in the United States.

Writing in the journal Nature, the team explain that patients often develop resistance to colorectal cancer drugs that target epidermal growth factor receptors (EGFRs). The team show in cell-line models that KRAS mutations can cause resistance to an anti-EGFR therapy called cetuximab. These mutations can either be acquired during treatment or may have pre-existed in a small fraction of tumour cells before treatment.

Two of the Italian study authors, Professor Alberto Bardelli from the Institute for Cancer Research and Treatment in Turin and Salvatore Siena from the Falck Division of Medical Oncology at the Niguarda Ca' Granda Hospital in Milan, were supported by the EU-funded COLTHERES ('Modelling and predicting sensitivity to targeted therapies in colorectal cancers') project which received EUR 5,999,300 of funding under the 'Health' Theme of the EU's Seventh Framework Programme (FP7).

Professor Bardelli comments: 'Emergence of secondary resistance to anti EGFR therapies (disease progression) in colorectal cancers is presently established by radiological evaluation. In the paper we describe for the first time that KRAS gene alterations are a mechanism of acquired resistance to anti EGFR therapies in CRCs and occur in approximately 50% of patients.'

The findings in this latest study come at the same time as a second team of researchers publish results demonstrating that resistance mutations in KRAS and other genes are highly likely to be present in a subpopulation of tumour cells before treatment. In this complementary study, also published in Nature, researchers from Austria, China and the United States show that these mutations can be detected months before there is clinical evidence of treatment failure, which could provide a signal to start alternative treatments.

These researchers used mathematical modelling to provide evidence that KRAS mutations pre-exist in tumour cells before treatment with the anti-EGFR treatment panitumumab. This may explain why clinical recurrence usually occurs within the same timescale, about 5 to 7 months after treatment began.

Both studies show that DNA from these mutations can be detected in liquid biopsies several months before radiographic evidence of disease

progression is observable. The hope now is that scientists will be able to build on these results by using combination therapy to anticipate and counter resistance before patients relapse.

Professor Bardelli explains that both study groups demonstrate that these mutations can be detected in plasma using an approach called 'liquid biopsy'.

He adds: 'This means that it is now possible to monitor the evolution of the tumour in response to therapy using a blood draw to detect early mutations that drive acquired resistance. The concept of liquid biopsy is an important step forward in the field. It was already known that the measurement of circulating tumour free DNA in the blood of patients could be used to monitor tumour burden. Our work shows that molecular determinants of acquired resistance can be detected several months before the clinical manifestation of relapse.'

Professor Bardelli also notes that it is important to clarify that what they have discovered is 'not a novel way to detect colon cancer' rather they have found a strategy to non-invasively detect early relapse from therapy in colorectal cancer patients.

As well as Italy, COLTHERES, which started in 2011 and runs until 2014, supports researchers from Belgium, the Netherlands, Spain, Switzerland and the United Kingdom, and its central aim is to help develop knowledge in the 'personalised' approach to cancer treatment where the 'right' combination of drugs is administered to the 'right' patients, based on a detailed understanding of their genetic background.

Some of the issues the COLTHERES project addresses are molecular profiling of colon cancer patient samples using multiple omics-based technologies for co-segregating lesions that could impart resistance to existing and emerging targeted therapies, and building and screening

predictive in vitro models based on this data to enable the rapid and empirical determination of drug resistance biomarkers.

For more information, please visit:

More information: Misale, S., et al. *Nature*, 2012. doi:10.1038/nature11156

Provided by CORDIS