Pharmacogenomic profiling and synthetic lethality screening in isogenic colorectal cancer cells carrying individual KRAS alleles

The advent of the EGFR-targeted monoclonal antibodies cetuximab and panitumumab has paved the way for individualized treatment of metastatic colorectal cancer (mCRC). Results from a number of clinical trials have demonstrated that oncogenic mutations affecting KRAS confer clinical resistance to these drugs. KRAS mutations are present in approximately 35-40% of colorectal cancer (CRC) samples. Of these, over 70% consist of alterations affecting codon 12 and about 20% are found at codon 13 (with G13D changes being by far the most prevalent).

Previous studies including small patient cohorts have occasionally reported that few patients with KRAS mutant tumors received clinical benefit from treatment with cetuximab or panitumumab. We noted that these unusual clinical responses were observed in patients affected by tumors carrying the KRAS G13D change. For this reason, we hypothesized that oncogenic alleles affecting KRAS codons 12 or 13 would result in different response to anti-EGFR monoclonal antibodies. In collaboration with a number of clinical units, we studied the effects of the G13D vs. other *KRAS* mutations in a pooled dataset of 579 chemotherapy-refractory colorectal cancer patients treated with cetuximab. We found that patients with p.G13D-mutated tumors treated with cetuximab had a longer overall and progression-free survival than patients with other KRAS mutated tumors.

To functionally evaluate the role of individual KRAS mutations in response to targeted therapies we introduced - by targeted homologous recombination - the seven most frequently mutated KRAS alleles in wild-type colorectal cancer cells. We found that cetuximab was able to impair proliferation of G13D mutated cells, while the growth of G12V clones was not affected. In addition, cetuximab administration prominently inhibited the growth of tumors formed by wild-type or KRAS G13D mutant cells grown as xenografts in immunocompromised mice. In contrast, the growth of tumors formed by KRAS G12V cells was not significantly delayed by drug treatment.

We then exploited these cellular models in functional genomic screens to identify genes or drugs that affect the survival of KRAS mutated cell lines. Using RNA interference to down-regulate gene expression we have defined a preliminary list of genes that preferentially suppress the growth of KRAS mutated cells.

Similarly, we have identified a number of compounds that may preferentially interfere with the growth of cells carrying specific KRAS mutations. These results must now be validated using independent experimental approaches.