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A Cervantes

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A BETTER UNDERSTANDING OF RESISTANCE TO ANTI-EGFRS IN NON-SMALL CELL LUNG CANCER

The way clones resistant to anti-EGFR (Epidermal Growth Factor Receptor) inhibition evolve in non-small cell lung cancer is far from being determined. In an international cooperative effort led by investigators at Johns Hopkins Hospital in Baltimore, the origin of acquired resistance mediated by the EGFRT^{790M} mutation has been further elucidated. That mutation, recognised as gatekeeper and present in about 60% of pretreated cases with anti-EGFRs, could occur either from the selection of previously existing EGFR^{790M} cell clones or by the evolution of originally EGFR^{790M}-negative drug-tolerant cells. In a series of elegant experiments, the authors show that these drug-tolerant cells have a diminished apoptotic response to third generation EFFR inhibitors specifically tackling EGFR^{790M}. Moreover, the use of potent inhibitors of the antiapoptotic factors BCL2 and BCL-xL, such as navitoclax, was able to restore sensitivity. Thus, drug-tolerant cells that are capable of surviving initial drug therapy may provide a reservoir of cells from which genetic mechanisms of acquired resistance can evolve. These data provide a rationale for developing novel strategies to tackle drug tolerant cells to prevent or delay the acquisition of resistance. These therapeutic approaches need to target both, drug-tolerant cells and the rare pre-existing drug resistant clones, at the same time. These findings may also help to design innovative trials potentially leading to improved patient survival.[1]

A POWERFUL TECHNOLOGY PLATFORM FOR PRECISION MEDICINE FOR PATIENTS WITH MELANOMA

Investigators from Cancer Research UK's Manchester Institute have developed a powerful technology platform to reinforce precision medicine in patients with melanoma. Whole exome sequencing, as well as targeted sequencing of circulating tumour DNA (ctDNA), were used to analyse responses to therapy and potential mechanisms of intrinsic or acquired resistance in more than 200 patients. Responses to BRAF and MEK inhibition were predicted in many instances by early decrease of the BRAF^{V600E} ctDNA levels. On the other hand, acquired resistance to the combination of BRAF and MEK inhibitors was detected by further increasing levels of the BRAF^{V600E} ctDNA, or by the appearance of NRAS^{Q61R} and NRAS^{Q61K}. The ctDNA analysis indicated relapses several weeks before imaging confirmation. Moreover, to complement liquid biopsies with a better strategy to provide effective second-line therapies, the authors developed the establishment of patient-derived xenografts, which was successful in 72% of cases. An interesting observation was made in a group of 80 individuals with non-V600 mutant BRAF melanomas. More than half carried V600 BRAF mutations and one had a K601 mutation, all known to be activating and potentially sensitive to BRAF inhibitors. In the rest, 21 had RAS mutations, three showed NF1 mutations and nine were wild type for BRAF, RAS and NF1. Another useful additional finding of this group was the potential for circulating tumour cells from patients to be tumourigenic and able to successfully induce xenografts in 15% of cases.[2]

MOLECULAR CHARACTERISATION OF AMPULLARY CANCERS

A cooperative effort by several academic institutions from Japan and the USA has helped to decipher the genetic landscape of ampullary neoplasms. These adenocarcinomas frequently show aggressive behaviour and are histologically characterised as being of an intestinal versus pancreatobiliary type. Therapy has so far been limited to surgery for localised disease and palliative chemotherapy when advanced disease is diagnosed. No targeted agents are currently approved for this type of tumour. The authors conducted an in depth analysis of the genomic alterations of ampullary carcinomas to establish a potential basis for new and more precise treatments. In fact, they sequenced

Biomedical Research Institute, INCLIVA, University of Valencia, Valencia, Spain

Correspondence to
Professor A Cervantes;
andres.cervantes@uv.es

172 clinically well-characterised ampullary carcinomas. The authors studied a discovery set cohort of 60 patients and a validation cohort to further confirm the initial findings. The mutated driver genes identified in the 60 ampullary carcinomas included KRAS, TP53, APC, ELF3, SMAD4, CTNNB1 and MUC4. Sequencing data demonstrated that ELF3 mutations are present at relatively high allele frequencies, implying that ELF3 mutation may represent an early event or a founder mutation in ampullary carcinomas. ELF3 silencing in normal epithelial cells enhances their motility and invasion. There were differences between the genomic landscapes of the intestinal phenotype and those of the pancreatobiliary phenotype. Among the significantly mutated genes, high-ranking genes based on the prevalence of mutations were similar between intestinal-type ampullary carcinomas and colorectal carcinomas (APC, TP53, KRAS and SMAD4) and between pancreatobiliary type carcinomas and pancreatic carcinomas (KRAS, TP53 and SMAD4). Potentially therapeutic targetable mutations in ERBB2, ERBB3, BRAF, BRCA2, PIK3CA and others, were identified in 51% of patients with ampullary carcinomas. No differences across racial background were observed. Multi-region exome sequencing clarified clonal evolution. The authors speculate that ampullary carcinomas will be good candidates for a personalised approach to therapy based on the genetic changes in these patients' cancers.[3]

Competing interests None declared.

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