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Colorectal cancer (CRC) is the second most commonly diagnosed cancer. CRC represents the second most common cause of deaths worldwide. Approximately 30% of patients with CRC have metastatic disease at the time of diagnosis (mCRC).

KRAS mutations screening is performed in cases of metastatic colorectal cancer (mCRC) for therapeutic decision making.

Several studies showed the presence of a hotspot mutation in codons 12, 13, 61 and 63 in KRAS oncogene.

KRAS mutation status allows for the identification of patients who might benefit from anti-EGFR therapies and avoid a costly and potentially toxic administration of this treatment in non-responsive patients.

Wild-type KRAS status:
- Responsive to anti-EGFR therapies
- Mutated KRAS:
  - Non-responsive to anti-EGFR therapies

Scientific background

Somatic mutations in the RAS oncogene family (HRAS, KRAS and NRAS) are observed in a variety of malignancies, including colorectal cancer (33–53%), pancreatic cancer (~80%), lung adenocarcinoma (~30%), ovarian and endometrial cancer, gall bladder cancer, bile duct cancer (~45%), thyroid cancer (~55%) and hematological malignancies.

The KRAS gene is located on chromosome 12 and encodes a G protein involved in colorectal carcinogenesis. The KRAS protein plays a central role in tumor development, regulating downstream proteins involved in proliferation, survival, metastasis and angiogenesis via the EGFR signalling pathway.

The KRAS protein regulates PI3K/AKT and RAS/MEK/ERK signalling pathways located downstream of many growth factor receptors, including EGFR. When bound to its ligand, EGFR stimulates tyrosine kinase activity leading to activation of KRAS and downstream signalling pathways. Genetic alterations of the intracellular effectors involved in EGFR-related signalling pathways may have an effect on response to this targeted therapy. The presence of an activating mutation in codons 12 and 13, the KRAS protein is permanently turned on, even without being triggered by EGFR mediated signalling and the therapies targeting EGFR are ineffective.

Specific target-directed therapies

3 monoclonal antibodies have been approved for colorectal cancer therapy including monoclonal antibodies against epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF).

The new therapies targeting EGFR are cetuximab (Erbitux®, Merck Serono) and panitumumab (Vectibix®, Amgen). The action of cetuximab or panitumumab is the blockage of ligand-binding receptor and thereby causing the inhibition of ligand mediated pathway.

The European Commission has granted a market authorization for cetuximab and panitumumab for the treatment of patients whose tumors harbor normal, non-mutated (wild type, WT) KRAS gene.

Additional advances in bio marker use for direct target therapies

BRAF and POUK mutations are being explored and seem to give promising data for a more accurate therapeutic approach.