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Editorial:

MUTATIONAL ANALYSIS OF K-Ras IN METASTATIC COLORECTAL CANCERS AND THERAPEUTIC IMPLICATIONS.

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Version española

Three human *Ras* proto-oncogenes encode small GTPases (HRas,N-Ras, K-Ras4A and K-Ras4B) that operate as binary molecular switches that cycle between an inactive GDP-bound form and an active GTP-bound form at the membrane[1]. K-Ras is localizated in cromosome 12p12 and has 45 Kb in extension[2]. The protein codificated by this gene have a structural conformation with 21 Kd in cytoplasm membrane.

Each GTPase has the capacity to transduce signals from cell-surface receptors into the cytoplasm through specific effector pathways that regulate cell growth, differentiation and apoptosis[3], [4].

Ras in an active conformation depends on the rates of GDP/GTP exchange. When Ras is bound to GDP is inactive and when it is bound to GTP is active[5].Guanine-nucleotide exchange factors (GEFs) bind to Ras and markedly accelerate the rate of GDP dissociation. By contrast, deactivation requires the binding of GTPase-activating proteins (GAPs) that significantly enhance the intrinsic GTPase activity. A defective 'off' switch in this cycle has major implications for human disease. Proteins that have specific point mutations that render the GTPase insensitive are locked in the GTP-bound state, causing aberrant downstream signalling[6].This can promote cell proliferation and

protection from apoptosis; indeed, approximately 30% of human cancers contain mutation in Ras genes.

The mutations are common in colorectal cancer, pancreatic cancer, lung adenocarcinoma, gall bladder cancer, bile duct cancer and thyroid cancer. Also can indicate prognosis and may be predictive of drug response. The crucial alterations of the K-Ras gene which are responsible for malignant transformation are point mutations in codons 12, 13 and 61 7, 8.

One of the most promising targets in mCRC is the epidermal growth factor receptor (EGFR), which is activated in colorectal carcinogenesis by the binding of a ligand on the extracellular part of it. The autophosphorylation of the intracellular tyrosine kinase domain of the EGFR activates downstream signaling pathways, including the Ras pathway, which interfere with apoptosis, cell proliferation, angiogenesis, and the metastatic process.

In particular, recent publications have shown that the successful treatment of metastatic Colorectal Cancer (mCRC), using monoclonal antibody therapies such as Panitumumab or Cetuximab, is directly linked to the oncogenic activation of the K-Ras signalling pathw9, 10, 11, 12.This monoclonal antibodies directed against the epidermal growth factor receptor (EGFR): Cetuximab is a chimeric antibody while Panitumumab is fully human.

Recent studies have suggested that mutations in K-Ras in tumors may impact the clinical response to Panitumumab. The efficacy in mCRC is confined to patiens with tumors lacking K-Ras mutations. Wild type K-Ras patients receiving Panitumumab have better CRC symptoms versus best supportive care patients. On the other hand there is no difference between patients treated with best supportive care and Panitumumab patients when they have K-Ras mutation13.

Panitumumab and Cetuximab improves overall survival and progression-free survival and preserves quality-of-life measures in patients with colorectal cancer in whom have no K-Ras mutations. As, wild type K-Ras is required for efficacy in patients with mCRC, K-Ras status should be considered in selecting patients with as candidates for Panitumumab or Cetuximab therapy.

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