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Editorial

Resistance to anti-EGFR targeted therapy mediated by oncogenetic mutations in colorectal cancer: Revision of the dogma?

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Traditionally, systemic treatment for high stage colorectal carcinoma (CRC) is mainly fluorouracil-based chemotherapy [1]. The anti-epidermal growth factor receptor (EGFR) monoclonal antibodies, by acting on specific molecular pathways in tumor growth or modulating immune response towards tumor cells, provide a more targeted response, a better side effect profile and greater impact on patient survival compared with conventional molecules. This monoclonal antibody that binds the extracellular domain of epidermal growth factor receptor, is known to be effective only in a subset of KRAS wild-type colorectal cancers.

Patients with mutations in either KRAS or NRAS gene are not eligible for anti-EGFR monoclonal antibody therapy [3]. This is due to downstream activation of the Ras/Raf/MAPK pathway by mutated RAS protein, leading to cell proliferation which cannot be sufficiently inhibited by anti-EGFR receptor monoclonal antibodies [4]. With the increasing choices of targeted agents, more and more biomarkers are tested. Currently, the standard recommended biomarker panel for colorectal carcinoma would include KRAS, NRAS, BRAF gene hotspot mutation detection and microsatellite instability test [5].

With the advances in genomic profiling and sequencing and the understanding of the resistance mechanisms, the contraindication of anti-EGFR therapy in mutant KRAS patients may be revised.

Based on the fact that the KRAS mutation in CRC suppresses the phosphorylation of the AMP-activated protein kinase (AMPK) known to be toxic for the tumor cells, Hua et al obtained a satisfactory response to for the anti-EGFR antibodies in mutant KRAS CRC xenograft models after reactivation of the AMPK [6]. Knickelbein et al demonstrated that the anti-EGFR antibodies induce the death of CRC cells via a p73-dependent transcriptional activation of the pro-apoptotic Bcl-2 family protein (PUMA). This action is abolished in case of KRAS mutation. These authors admitted that the restoration of this pathway by inhibiting aurora kinases preferentially kills mutant KRAS CRC cells and overcomes KRAS-mediated resistance to anti-EGFR antibodies [7]. In fifty-one CRC patient-derived xenografts study, Lee et al showed that KRAS mutants expressed remarkably elevated autocrine levels of high-affinity EGFR ligands compared with wild-type KRAS. The use of an anti-EGFR IgG1 antibody that displays potent inhibitory effects on high-affinity EGFR ligand enhanced CRC KRAS mutant cells cytotoxicity [8].

Dealing with the resistance to targeted therapies in CRC patient looks feasible. It could allow to broaden the indications of anti-EGFR therapy and provide a better survival for a larger group of CRC patients. In this era of precision and personalized medicine, a complete case specific tumor profiling and the comprehensive study of the tumorogenesis mechanisms should allow to overcome the intrinsic and acquired resistance to these targeted high effective therapies.

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