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Autor(en) des Beitrags: Gasch, Christin; Bauernhofer, Thomas; Pichler, Martin; Langer-Freitag, Sabine; Reeh, Matthias; Seifert, Adrian M; Mauermann, Oliver; Izbicki, Jakob R; Pantel, Klaus; Riethdorf, Sabine

Titel des Beitrags: Heterogeneity of epidermal growth factor receptor status and mutations of KRAS/PIK3CA in circulating tumor cells of patients with colorectal cancer.

Abstract: Molecular characterization of circulating tumor cells (CTCs) is pivotal to increasing the diagnostic specificity of CTC assays and investigating therapeutic targets and their downstream pathways on CTCs. We focused on epidermal growth factor receptor (EGFR) and genes relevant for its inhibition in patients with colorectal cancer (CRC). We used the CellSearch® system for CTC detection in peripheral blood samples from 49 patients with metastatic CRC (mCRC) and 32 patients with nonmetastatic CRC (nmCRC). We assessed EGFR expression in 741 CTCs from 27 patients with mCRC and 6 patients with nmCRC using a fluorescein-conjugated antibody with the CellSearch Epithelial Cell Kit. DNA of a single CTC isolated by micromanipulation was propagated by whole-genome amplification and analyzed by quantitative PCR for EGFR gene amplification and sequencing for KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog), BRAF (v-raf murine sarcoma viral oncogene homolog B1), and PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit ?) mutations. At least 2 CTCs were detected in 24 of 49 patients with mCRC and 7 of 32 patients with nmCRC. In 7 of 33 patients, CTCs
with increased EGFR expression were identified. Heterogeneity in EGFR expression was observed between CTCs from the same patient. EGFR gene amplification was found in 7 of 26 CTCs from 3 patients. The investigated BRAF gene locus was not mutated in 44 analyzed CTCs, whereas KRAS mutations were detected in 5 of 15 CTCs from 1 patient and PIK3CA mutations in 14 of 36 CTCs from 4 patients. Molecular characterization of single CTCs demonstrated considerable intra- and interpatient heterogeneity of EGFR expression and genetic alterations in EGFR, KRAS, and PIK3CA, possibly explaining the variable response rates to EGFR inhibition in patients with CRC.