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Abstract 2913: Emergence of *RAS* or *EGFR* mutant clones affects duration of response to EGFR blockade in colorectal cancers

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Abstract

Cetuximab and panitumumab are monoclonal anti-EGFR antibodies (moAbs) currently used for the treatment of advanced RAS wild type colorectal cancers (CRC). Emergence of acquired resistance invariably limits the efficacy of these agents, and the dynamics of clonal evolution during anti-EGFR blockade are poorly understood. At progression, RAS mutations represent the most common genetic alterations, while EGFR extracellular domain (ECD) mutations are acquired by a smaller cohort of patients. We found that the mutation profile correlates with the clinical outcome of patients; in particular those who develop RAS mutations upon EGFR blockade achieve reduced tumor shrinkage and shorter duration of response respect to patients in which EGFR ECD mutations emerge during therapy. We investigated in preclinical models the potential role of RAS and EGFR ECD mutations during the emergence of acquired resistance, by tracking the evolution of clones in a genetically barcoded population of CRC cells chronically treated with cetuximab. We observed that therapeutic (target therapy, chemotherapy) and environmental (reduced nutrient condition) pressures differentially shape the clonal composition of CRC cell populations, leading to the emergence of clones with the highest fitness in presence of the external pressure. In conclusion, a multistep clonal evolution process characterizes the development of drug resistance and is associated with the clinical outcome of CRC patients treated with anti-EGFR antibodies.

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