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A combined computational and functional approach identifies IGF2BP2 as a driver of chemoresistance in a wide array of pre-clinical models of colorectal cancer

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Abstract

Aim Chemoresistance is a major cause of treatment failure in colorectal cancer (CRC) therapy. In this study, the impact of the IGF2BP family of RNA-binding proteins on CRC chemoresistance was investigated using in silico, in vitro, and in vivo approaches.

Methods Gene expression data from a well-characterized cohort and publicly available cross-linking immunoprecipitation sequencing (CLIP-Seq) data were collected. Resistance to chemotherapeutics was assessed in patient-derived xenografts (PDXs) and patient-derived organoids (PDOs). Functional studies were performed in 2D and 3D cell culture models, including proliferation, spheroid growth, and mitochondrial respiration analyses.

Results We identified IGF2BP2 as the most abundant IGF2BP in primary and metastastatic CRC, correlating with tumor stage in patient samples and tumor growth in PDXs. IGF2BP2 expression in primary tumor tissue was significantly associated with resistance to selumetinib, gefitinib, and regorafenib in PDOs and to 5-fluorouracil and oxaliplatin in PDX in vivo. *IGF2BP2* knockout (KO) HCT116 cells were more susceptible to regorafenib in 2D and to oxaliplatin, selumitinib, and nintedanib in 3D cell culture. Further, a bioinformatic analysis using CLIP data suggested stabilization of target transcripts in primary and metastatic tumors. Measurement of oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) revealed a decreased basal OCR and an increase in glycolytic ATP production rate in *IGF2BP2* KO. In addition, real-time reverse transcriptase polymerase chain reaction (qPCR) analysis confirmed