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Abstract LB-299: A comprehensive platform of patient-derived xenografts and matched cell lines mirrors the genomic landscape of colorectal cancer FREE

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Abstract

Preclinical models that accurately reflect patients' tumor with regards to histopathology, genomics, and therapeutic response represent a compelling need to fuel the progress of effective cancer treatments. Patient-derived tumor xenografts (PDXs) have significantly accelerated this process, but, although they closely mirror structural and molecular features of the tumor of origin, they still retain important restrictions related to maintenance costs and large-scale screening. To overcome this issue, we have established a novel platform of 2D-cell lines (xeno-cell lines, XL) derived from PDXs of colorectal cancer (CRC) from which patient's germline gDNA was available. We have characterized XL-cells at multiple levels to confirm their proximity to the PDXs of origin and to assess their suitability as patient avatars *in vitro* to interrogate functional networks in colorectal cancer. All XL-cells showed an epithelial-like morphology and phenotype, as also confirmed by EMT biomarker transcriptomic analysis. Whole exome and RNA-seq analyses showed that genomic features were consistently preserved between PDXs and matched cell models. Expression analysis revealed the XL-line collection as a significant representative of all CRC subtypes (*CMS* and *CRIS* subgroups). Furthermore, genomic analysis allowed the identification of molecular biomarkers of response and resistance to targeted therapies, including EGFR and HER2 blockade. In particular, molecular determinants of resistance to dual-HER2 blockade previously reported in the Heracles-A trial were validated in XL-cells. In conclusion, the XL-cell line and PDX platform represents a unique and comprehensive preclinical tool to validate gene function e to identify novel pharmacological vulnerabilities in colorectal cancer.

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