Title: Genomic and transcriptomic factors underlying differential response to adjuvant chemotherapy in colorectal cancer

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Keywords:
Colorectal cancer, precision oncology, patient-derived tumor organoids, treatment response

Abstract
Precision oncology research in colorectal cancer utilizes patient-derived tumor organoids (PDTOs) as in vitro models to predict clinical outcomes, but such efforts are unfit to identify molecular factors underlying differential responses to therapy. Using an integrative approach, we linked the genomic (whole-exome sequencing) and transcriptomic (RNA sequencing) profiles of primary colorectal cancer tumors and matched PDTOs to the in vitro drug responses against standard-of-care chemotherapeutics fluorouracil, irinotecan, and oxaliplatin. We identified somatic mutations associated with differential drug responses in vitro, of which *CTNNB1* mutations were associated with higher sensitivity to fluorouracil and oxaliplatin. Differential expression analysis between PDTOs with high and low sensitivity to each drug revealed genes associated with chemoresistance. Gene set enrichment analysis (GSEA) for hallmark gene sets showed an association between interferon gamma response and low sensitivity to all three drugs, while epithelial-mesenchymal transition (EMT) and hypoxia were associated with high sensitivity. Overall, our results highlight the utility of PDTOs for identifying epithelial cell-specific molecular features contributing to poor in vitro drug responses in colorectal cancer, which can be targeted to develop more effective treatment strategies.