

Quantitative Evaluation of Colorectal Cancer Organoid Genomic and Transcriptomic Fidelity Using a Dual-Reference Divergence Framework

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Abstract

Patient-derived colorectal cancer (CRC) organoids are cornerstone models in translational oncology, yet distinguishing true tumor-specific evolution from in vitro culture artifacts across multi-omics profiles remains a critical methodological hurdle. Here, we establish a robust computational framework to systematically quantify copy number variation (CNV), gene expression divergence, and clonal heterogeneity across CRC patient cohorts. By integrating multi-metric genomic and transcriptomic profiles encompassing entropy, amplitude, directional alterations, and expression shifts against dual reference baselines, we uncover significant patient-specific divergence. Furthermore, our profiling identifies evolutionary hotspots of organoid selection, highlighting regions prone to in vitro adaptation in CRC models. Patient-specific composite aberration scoring successfully categorizes cohort heterogeneity and identifies high-divergence tumor models. This methodology provides researchers with an unbiased guideline for assessing organoid fidelity, uncovering evolutionary selection pressures, and enhancing the translational reliability of precision colorectal cancer models.

Index Terms

Colorectal Cancer, Patient-Derived Organoids, Genomic Fidelity, Evolutionary Selection, Clonal Heterogeneity