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Abstract

Multi-omics and drug response assessments in longitudinal patient avatars unveil patient-specific recurrence trajectories and drug susceptibilities in glioblastoma

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Introduction: Glioblastomas (GBMs) are the most aggressive adult brain tumors, with a median survival of 18 months despite standard treatments. GBMs undergo complex changes at recurrence, although no common evolutionary path has been found. Understanding molecular evolution could reveal changes in drug response. High-resolution multi-omics profiling and functional studies in matched patient avatars can provide clinically-relevant insights into tumour evolution at the individual patient level.

Materials and Methods: We analyzed longitudinal tumors and derived preclinical models from 8 patients, using organoids and orthotopic xenografts. We performed a comprehensive multi-omics profiling, including transcriptomics (bulk and single cell RNA-seq), epigenomics (DNA methylation arrays), genomics (targeted DNA-seq) and proteomics (LC-MS) to identify molecular evolution of tumors at recurrence. We further carried out an ex-vivo functional drug screen with a pharmacologically diverse 1482 compound library targeting cancer pathways and epigenetic modifiers.

Results and Discussion: High-resolution multi-omics analysis revealed patient-specific tumor evolution at recurrence. While certain GBMs recurred without major molecular adaptation, others showed significant (epi)genetic and transcriptomic evolution towards new genetic clones and/or transcriptomic states. Majority of drug responses were similar in primary and recurrent tumours and were patient-specific. Interestingly, we observed selective susceptibilities to several epigenetic modifiers, especially Histone Deacetylase (HDAC) and Aurora Kinase (AURK) inhibitors in certain primary tumours, which were lost at recurrence.

Conclusion: Our study highlights the value of combined omics and functional profiling in understanding GBM evolution and suggests that drug effectiveness may vary between primary and recurrent tumors, which has implications for precision therapy.