COMPLEX EVOLUTIONARY DYNAMICS GENERATES GENETIC DIVERSITY AND INTRA-TUMOR HETEROGENEITY IN INDIVIDUAL PATIENTS WITH GLIOBLASTOMA

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BACKGROUND: Glioblastoma (GB) is the most common and aggressive primary brain malignancy. The disease is advanced at the time of clinical presentation and response to treatment may be confounded by clonal heterogeneity and differential patterns of resistance in spatially distinct parts of the same tumor. However, we do not understand how this complex environment evolves. Accumulating evidence suggests that intra-tumor heterogeneity is likely to be the key to understanding treatment failure, however the dynamics of such heterogeneity are still poorly understood.

METHODS: Using a Fluorescence-Guided Multiple Sampling technique we obtained samples from the tumor mass, the sub-ependymal zone and the non-fluorescent tumor margin. We performed an integrated genomic analysis and combined copy number alteration and molecular clock data to develop a phylogenetic and spatial reconstruction of tumor evolution in individual patients.

RESULTS: Phylogenetic reconstruction of the fragments from each GB identifies copy number alterations in EGFR and CDKN2A/B/p14ARF as early evolutionary events while aberrations in PDGFRA and PTEN occur later in the disease progression. Transcriptional profiling reveals that many patients display multiple GB subtypes within their tumor while deconstruction of the clonal organization of each tumor fragment at single-molecule level identified multiple coexisting cell lineages. Ancestral tumor precursors that gave rise to the tumor mass were found in the sub-ependymal zone of a subset of GB patients. However, in two patients the disease evolved from ancestors that were spatially remote from the sub-ependymal zone.

CONCLUSIONS: Our integrated genomic analysis reports the evolution of GB in individual patients across multiple spatial scales. Our data reveals early clonal diversification generating a genetically complex and highly evolved disease environment at clinical presentation. We propose that these fundamental patient-specific tumor evolutionary dynamics underlie clinical phenotypic heterogeneity and may have implications for the emergence of resistant disease. SECONDARY CATEGORY: Neuropathology & Tumor Biomarkers.