Tracking Molecular Predictors of Glioma Evolution

by

Quanhua MU

Abstract
Even with intensive treatment including radiotherapy and chemotherapy, gliomas, the most common and aggressive brain tumor in adults, inevitably recur with elevated aggressiveness and treatment resistance. Our understanding of recurrent glioma and their evolution under treatment remain very limited.

We hypothesize that genomic alterations highly enriched or even specific in recurrent glioma contribute to their clinical characteristics. In the first study, we developed copy number prediction and gene fusion prioritization tools to analyzed RNA-sequencing data of temozolomide (TMZ) treated glioma. We found a subset of recurrent gliomas carrying MGMT genomic rearrangements that lead to MGMT overexpression and contribute to TMZ resistance. In the second study, we collected and analyzed DNA and/or RNA sequencing data of 188 secondary glioblastomas (sGBMs) to reveal their mutational landscape. We found METex14 presents in ~14% of sGBM cases with significantly worse prognosis. Subsequent studies show that METex14 promotes glioma progression by prolonging MET activity. Analysis of drug screening data suggests METex14 positive glioma cells are sensitive to MET inhibitors. Experiments and clinical trials from collaborators demonstrated the potential of precisely treating MET altered gliomas using a new MET inhibitor. Analysis of one case indicated PI3K pathway activation may contribute to MET inhibitor resistance.

In the third study we tested the hypothesis that features of the initial tumor predispose tumor recurrence. We collected and analysed sequencing and clinical data of initial-recurrent tumor pairs from 512 patients, among which 96 developed progression from lower-grade gliomas to glioblastoma and 67 developed therapy-driven hypermutation at relapse. To track early predictors of glioma evolution, machine learning models were developed to forecast evolutionary trajectories based on features collected at initial. Strikingly, we found MYC amplifications and transcriptional pathway activation at diagnosis predisposing hypermutations at recurrence, which was experimentally verified in perturbations of cancer cell lines. Furthermore, we showed that chromatin openness, transcription activity and c-Myc binding synergistically increase the vulnerability of genomic regions to TMZ-driven mutagenesis; and hence the MYC targets, including mismatch repair genes, tend to develop loss-of-function mutations leading to higher probability of hypermutation. This study underscores the potential of precise cancer management by predicting and targeting clonal dynamics.