THE P53 PATHWAY AND ANCESTRAL PROGENITORS ARE ASSOCIATED WITH TUMOR RECURRENCE IN GLIOBLASTOMA

BACKGROUND: The mechanisms driving glioblastoma (GBM) relapse remain elusive. To investigate evolutionary patterns in recurrence and therapy-resistance of GBM, we analyzed the genomic profiles from 252 primary GBM and 60 biopsy samples taken from 23 pairs of pre- and post-treatment GBM tumors.

METHODS: We integrated mutation allele fraction, DNA copy number and genotype information to determine the cellular frequencies of all mutations and found that 70.5% of mutations were classified as clonal and 30.5% as subclonal. We validated our classification approach through multi-sector sequencing of 13 GBM tumors.

RESULTS: Separating patients into discrete age groups by an interval of 10 years, we observed a significant linear correlation between clonal mutations and age ($P = 3.69 \times 10^{-7}$), but no correlation between age and subclonal mutations ($P = 0.62$). This result suggested that clonal mutations predominantly accumulated over the life span of the cell population that gave rise to the cell of origin before neoplastic onset, whereas subclonal mutations were acquired during tumorigenesis and may reflect intratumor heterogeneity. Interestingly, mutation or aneuploidy of p53 pathway members strongly correlated with increased fraction of subclonal mutations ($P = 6 \times 10^{-5}$, Wilcoxon rank test), unrelated to patient age. To further evaluate the association between TP53 mutation status, intratumoral heterogeneity and clonal evolution, we analyzed exome sequencing and DNA copy number data from 23 pairs of first and recurrent GBM tumors. We found that TP53 mutant GBM showed a significant increase in subclonal mutation frequency relative to the matched primary tumor ($P = 0.0015$). The clonal mutation frequency was unaffected ($P = 0.23$). These data suggested that TP53 mutant GBM became increasingly clonally complex at time of recurrence, whereas TP53 wildtype GBM showed a reduced level of intratumoral heterogeneity. To comprehensively investigate tumor recurrence we performed whole genome sequencing of seven primary-recurrent tumor pairs. We found that major clones in the tumor recurrence resembled major clones in the matching primary, and were both derived from an ancestral cell population. The same applied to minor clones, suggesting that multiple types of ancestral cells existed. CONCLUSIONS: We showed that mutations in the p53 pathway resulted in increased intratumoral heterogeneity at time of diagnosis and after tumor recurrence. Disease relapse was fueled by ancestral cell populations. Further research is needed to determine the impact of intratumoral heterogeneity on treatment response. Our study provides a molecular snapshot of tumor evolution in glioblastoma.

SECONDARY CATEGORY: Neuropathology and Tumor Biomarkers.