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Presentation Abstract

Abstract Number:	984
Presentation Title:	Alteration of the p53 pathway is associated with subclonal tumor progression in glioblastoma
Presentation Time:	Sunday, Apr 06, 2014, 3:50 PM - 4:05 PM
Location:	Room 5, San Diego Convention Center
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Abstract Body:	To evaluate evolutionary patterns in progression and therapy-resistance of GBM, we analyzed the genomic profiles of 252 GBM samples from The Cancer Genome Atlas (TCGA)1, including 48 multi-sector and recurrent tumor biopsies taken from 17 pairs of pre- and post-treatment GBMs, to understand 1) the intratumoral heterogeneity of GBM and 2) how GBM responds to therapeutic intervention. We integrated variant allele fraction, DNA copy number and genotype information to determine clonality of all mutations and found that 69.5% of mutations (median across samples 70.1% ± 19.6%) were classified as clonal and 30.5% as subclonal. To verify our classification approach, we classified mutations detected in two non-overlapping biopsies from 11 tumors into clonal and subclonal categories. Of mutations detected in both tumor sectors 86.2% were classified as clonal and 45.2% of sample-private mutations were categorized as clonal, which was a strongly significant difference (P = 1.8×10-87). Separating patients into discrete age groups by an interval of 10 years, we found a significant linear correlation between clonal mutations and age (P < 0.001). This observation supports the notion that clonal mutations predominantly accumulated over the life span of the cell population that gave rise to the cell of origin before neoplastic onset2. No correlation with age was found for subclonal mutations. In contrast, the frequency of subclonal mutations was strongly correlated with the presence of alterations related to the p53 pathway (P < 0.001), particularly TP53 point mutation or amplification of MDM2. This observation raises the possibility that p53 pathway alterations stimulate subclonal evolution, possibly by providing greater tolerance to DNA damage and/or suppression of apoptosis3. To evaluate the effects of clonal heterogeneity on disease recurrence, we analyzed matched pairs of primary and recurrent GBM, including five pairs with mutated TP53 and nine pairs with wildtype TP53. Recurrent TP53 mutant GBM showed a further and significant increase in the subclonal mutation frequency. In contrast, TP53 wildtype tumors showed an increase in the frequency of clonal mutations compared to their matched primary tumor. These data suggest that TP53 mutant GBM became increasingly clonally complex at time of recurrence, whereas TP53 wildtype GBM showed a reduced level of intratumoral heterogeneity. We observed an ultramutator phenotype in three recurrent tumors, associated with temozolomide treatment. Our results suggest that mutations in the p53 pathway affect the response to therapy by supporting greater intratumoral heterogeneity. Paradoxically we observe a trend towards improved event free survival in samples with high subclonal mutation frequency. Further research is needed to assess whether the level of intratumoral heterogeneity is a reflection of the molecular portrait of GBM progression.

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