

Exploration of biomarkers to predict anti-glioma stem cells effect by a Sonic hedgehog inhibitor

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Background: Lower grade gliomas (LGGs, WHO grade II/III gliomas) account for approximately one third of all gliomas. Although LGGs are typically slowly progressive, their clinical course is invariably indolent and most patients ultimately succumb to death. In contrast to glioblastoma, our knowledge about the genetic lesions and clonal evolution in LGG is still incomplete.

Methods: To obtain a complete registry of gene mutations involved in LGG pathogenesis and their role in clonal evolution, we analyzed whole exome sequencing and/or targeted sequencing of 757 LGG cases from Japan and the Cancer Genome Atlas consortium. Clonal evolution in LGG was investigated using multi-time point/regional sampling in 14 cases with LGGs.

Results: Massive parallel sequencing revealed LGGs were clearly grouped into three subgroups with or without *IDH1/2* mutation and 1p/19q loss of heterozygous (LOH). Type I tumor with *IDH1/2* mutation and 1p/19q LOH had a most favorable survival and harbored mutations in *TERT* promoter, *CIC*, *FUBP1* and *NOTCH1*. Type II tumor with *IDH1/2* mutant/1p19q intact subtype represented *TP53* biallelic inactivation and/or *ATRX* mutations. Type III tumor with *IDH1/2* intact showed GBM like mutation profile and poor prognosis.

Large scale samples allowed to obviously detect strong positive/negative correlations with each other driver genes. Extensive analysis of variant allele frequencies among co-existing mutations revealed temporal orders of gene mutations in each subtypes.

Multi regional/time-points sampling analysis supported mutational order and revealed a close correlation of regional heterogeneity with the history of clonal evolution, illustrating the way by which a tumor expands from its origin to surrounding regions, while increasing intratumor heterogeneity and spatially intermingling different evolutionary branches in periphery.

Conclusion: Our findings delineated the landscape of gene mutations in LGG. LGG had mutually exclusive mutational patterns with hierarchical order in discrete subtypes. LGG contiguously developed and generated heterogeneity through acquiring new mutations in a complex but ordered fashion. Prominent regional heterogeneity raises a potential concern that sequencing of bulk tumor may not detect rare, but important mutations.