Neuro-Oncology 18:iii1–iii6, 2016.
doi:10.1093/neuonc/now065.20

NEURO-ONCOLOGY

Abstracts

AT-21. INTEGRATED (EPI)GENOMIC ANALYSES IDENTIFY SUB-GROUP SPECIFIC THERAPEUTIC TARGETS IN CNS RHABDOID TUMORS

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Atypical Teratoid Rhabdoid Tumors (ATRTs) are the most common malignant embryonal brain tumors arising in younger children that are distinctly lethal cancers for which effective therapies are lacking. In this study, we integrated whole genome/exome/transcriptome sequencing as well as methylation and nucleosomal profiling analyses to comprehensively define the genomic and epigenomic landscape of ATRT sub-groups and identify sub-group specific therapeutic targets. Integration of multiplatform genomic analyses revealed novel recurrent genetic alterations in upto 20% of ATRTs in genes with functions in neural development and epigenetic regulation. Global methylation and gene expression analyses of primary tumors indicated segregation of ATRTs into three epigenetic sub-groups (group 1, 2A and 2B) that correlated with distinct lineage and clinical features. Group 1 ATRT exhibited enrichment of neurogenic/NOTCH signaling loci and were predominantly supra-tentorial tumors with a median age of 24 months. Group 2A tumors were predominantly infra-tentorial locations in the youngest patients, while group 2B tumors were characteristically spinal in location. BMP signaling and mesenchymal differentiation genes were commonly enriched in group 2A and 2B tumors. ATAC-seq analyses revealed a chromatin landscape associated with each ATRT sub-group, that correlated with sub-group specific therapeutic response in ATRT cell lines to a panel of signaling (NOTCH, BMP, Dasatinib) and epigenetic (EZH2, G9a, BRD4) inhibitors. Significantly, we discovered that differential methylation of a novel, PDGFRβ associated enhancer element confers robust sensitivity to tyrosine kinase inhibitors Dasatinib and Nilotinib in group 2 ATRTs, and suggest these as novel agents for this highly lethal ATRT sub-type.