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The consequences of *SMARCB1* loss in Atypical Teratoid Rhabdoid Tumors (ATRTs) have been extensively characterized at the epigenetic/transcriptomic level. In this study we detail the functional effect of *SMARCB1* mutation on the MRT proteome, its relationship with RNA deregulation or lack thereof. We performed unlabeled discovery proteomics using MS-SWATH on MRT cells in which SMARCB1 was forcibly re-expressed (5 cell lines, +/-SMARCB1); analyzing changes in protein abundance within 3 fractions (total, membrane, nuclear). We generated a custom spectral library, covering >8,000 proteins, for analysis of the ATRT proteome using a pH fractionated pool of each cellular subfraction. This SMARCB1-dependent ATRT spectral library constitutes a powerful tool for profiling proteins of potentially therapeutic relevance in both model systems and primary ATRT samples. We show that whilst gene expression and protein abundance are significantly related there are many instances whereby expression changes do not reliably predict protein abundances. Several hundred proteins show significantly increased abundance ($p<0.01$) with no concomitant change by RNA-seq. *SMARCB1* mutation is able to invoke critical changes in post-transcriptional/translational regulation as well as sub-cellular localization. By integration with whole-genome CRISPR/cas9 screening we describe functionally essential SMARCB1 dependent pathway/membrane biomarkers, evident at the protein but not the RNA level. We describe several which are druggable and suggest certain therapeutic modalities e.g. specific combinations of RTKs, RNA-binding proteins/splicing factors (SpliceosomeA, U4:U5:U6 tri-snRNP complexes). Our analysis links, for the first time in ATRT, genome-wide transcriptomic and proteome aberrations and reveals broad mechanisms underlying the effect of *SMARCB1* mutation.

ATRT-26. META-ANALYSIS OF TREATMENT MODALITIES IN METASTATIC ATYPICAL TERATOID/RHABDOID TUMORS IN CHILDREN

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BACKGROUND: Metastatic atypical teratoid/rhabdoid tumors (AT/RT) are aggressive central nervous system tumors that present during infancy and are associated with dismal outcomes. Patients receive multimodal treatment including surgical resection, systemic chemotherapy and one or more of intrathecal chemotherapy (IT), marrow-ablative chemotherapy with autologous hematopoietic cell rescue (AuHCR) and radiation therapy (XRT). While data regarding treatment modalities for AT/RT patients exist, no comprehensive data have been published regarding the metastatic patient population. METHODS: We performed a meta-analysis of 1,578 articles published through September 2018, including 44 studies with a total of 123 subjects. Additionally, seven patients were incorporated through chart review of patients treated at Nationwide Children's Hospital. RESULTS: Analysis of 130 patients revealed a 3-year overall survival (OS) of 25%. Age at diagnosis had a significant impact on survival ($p=0.0355$); 3-year OS for infants < 18 months was 21%; 18–36 months was 26%; and > 36 months was 36%. Location of the primary tumor, metastatic stage and extent of surgical resection did not have significant impact on OS. On univariate analysis, XRT ($p<0.0001$), IT ($p=0.01$) and AuHCR ($p<0.0001$) were found to significantly improve survival. The most substantial effect was noted in patients who received AuHCR (3-year OS of 60% *versus* 9% in those who did not). On multivariable analysis XRT ($p=0.0006$), IT ($p=0.0124$) and AuHCR ($p<0.0001$) were independently associated with reduced risk of death.

ATRT-27. COST-EFFECTIVE ASSAYS TO SUBGROUP ATRT IN THE DAILY ROUTINE

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Three atypical teratoid rhabdoid tumors (ATRT) molecular subgroups with different bio-clinical characteristics have been reported (TYR, SHH and MYC). Molecular subgrouping relies on either methylation profiling (reference methods), or expression profiling. However, the cost-effectiveness of such pangenomic screening is questionable. This work aims to study the reliability of alternative techniques for subgroup classification in the daily routine. Illumina EPIC-arrays were performed on 46 samples. Among those cases, expression profiling were analysed by RNAseq (n=30). We designed a 26-gene panel to assess expression profiling using the Nanostring technology; this was applied to 35 tumors. Immunohistochemistry (IHC) was used for 20 samples; it relied on the expression of MITF, TYR, OTX2 and MYC. We first assessed the concordance between DNA methylation and RNAseq based profilings; then, between RNAseq and Nanostring and, finally, between methylation profiling and Nanostring or IHC, the two rapidest and cheapest tools. The concordance between the two expression-based profiling was 19/21. EPIC-arrays and RNAseq or Nanostring were concordant in 26/30 and 30/35 samples, respectively. The concordance was perfect for methylation-defined MYC subtype. Finally, 17/20 tumor samples were classified in the same subgroup by EPIC-arrays and IHC; the 3/20 misclassified tumors were SHH by methylation but consistently MYC by IHC, Nanostring and RNAseq. There was 90–100% of concordance for TYR subgroup (all techniques). We have designed a gene panel-based expression signature that shows promising concordance with RNAseq and methylation profiling. Nanostring assay and IHC well predict ATRT subgroup classification for MYC and TYR subclass, but less so for methylation-defined SHH ones.

ATRT-28. SINGLE NUCLEI SEQUENCING REVEALS THE DIFFERENT PHENOTYPIC COMPOSITION OF THE ATRT SUBGROUPS

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Atypical teratoid/rhabdoid tumors (ATRT) represents a genomically homogeneous disease characterized by loss of SMARCB1 protein in the vast majority of cases. In recent years, it has become clear that these tumors display a high degree of intertumoral heterogeneity with three molecularly distinct subgroups. However, the degree of intratumoral heterogeneity and the information on cellular subpopulations currently remains largely an uncharted territory. To explore the transcriptomic composition of ATRTs, we performed single nuclei RNA sequencing for 16 ATRTs representing all three molecular subgroups (5 ATRT-TYR, 7 ATRT-SHH, 4 ATRT-MYC). By performing tSNE cluster analyses of all the single cell data (~50.000 cells have been sequenced), we were able to gain unprecedented insights into the phenotypic composition of ATRTs and unravelled substantial differences between the three subgroups. Integrating transcriptomic information from non-neoplastic brain cells and the data derived from single nuclei sequencing, we found an OPC like gene signature in ATRT-SHH. In contrast, ATRT-TYR subpopulations overexpressed more markers of neuronal stem cells suggesting a larger fraction of undifferentiated cells in this subgroup. We also identified a subpopulation of cells with a clear overexpression of cell cycle associated genes (CDK4, CDKN3), predominantly present in ATRT-MYC samples, a finding which may harbour important consequences for a targeted therapy with e.g. CDK inhibitors. In summary, our analyses reveal different cellular compartments in ATRT and provide important insights into the cellular differentiation of the three ATRT-subgroups. Further analyses to achieve a specific mapping of ATRT to its physiological cell of origin are currently being pursued.

ATRT-30. RETROSPECTIVE ANALYSIS OF CHILDREN WITH ATYPICAL TERATOID RHABDOID TUMOR TREATED ACCORDING TO ACNS0333

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Atypical teratoid rhabdoid tumor (ATRT) is a central nervous system tumor with poor outcome. ACNS0333, a Children's Oncology Group phase 3 trial, enrolled 65 evaluable patients who received two cycles of induction chemotherapy, three cycles of consolidative high-dose chemotherapy (HDCT), and focal radiation therapy (RT) pre- or post-consolidation. Craniospinal irradiation (CSI) was left to clinician discretion. We retrospectively analyzed medical records of 27 children treated at our institutions according to ACNS0333. Median age at diagnosis was 14 months (range 4–165); 13 (48%) were male. M-stage was M0, M2, and M3 for 18 (66%), 5 (19%), and 4 (15%), respectively. Tumor location was supratentorial (n=14, 52%), infratentorial (n=12, 44%), or both (n=1, 4%). Complete resection was achieved for 17 (63%). All but one completed induction. Of 13 (51%)