ously resilient against radiation therapy. Furthermore, wtIDH1 and IDH2 represent a unique target in radiation-resistant MB which has not previously been identified. Wild type IDH1/IDH2 are more recently shown to promote tumor proliferation and mediate metabolic reprogramming through the production of oncometabolites and substrates that functionally alter chromatin structure and gene transcription. We hypothesized that MYC modulation of wtIDH1/IDH2 facilitates metabolic reprogramming and promotes radiation-resistant cell populations. We show the change in the structural integrity of chromatin altered in radiation-resistant MB by metabolic adaptation and the effect of disrupting IDH1/IDH2 activity. We further compare these results to the chromatin profile of patient primary and matched relapsed MB samples at the single-cell level. We demonstrate that targeting IDH1/2 with chemical inhibitors suppresses MB cell growth. Our results disclose insights into the development of radiation resistance and provide a potential therapeutic target for the treatment of relapsed MYC-MB.

MEDB-71. MOLECULAR CHARACTERISATION OF GROUP 4 MEDULLOBLASTOMA IMPROVES RISK-STRATIFICATION AND ITS BIOLOGICAL UNDERSTANDING

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Group 4 (MB_{Grp4}) accounts for ~40% of medulloblastoma and the majority of non-WNT/non-SHH cases, yet its underpinning biology is poorly understood, and survival outcomes are not sufficiently explained by established clinicopathological risk factors. We investigated the clinical and molecular correlates of MB_{Grp4}, including second-generation methylation non-WNT/non-SHH subtypes (I-VIII) and whole chromosome aberration (WCA) subtypes (defined by chromosome 7 gain, 8 loss, and 11 loss; WCA-favourable risk [WCA-FR] ≥2 features, WCA-high risk [WCA-HR] ≤1 feature). A clinically-annotated MB_{Grp4} discovery cohort (n=378) was assembled from UK CCLG institutions, collaborating centres and SIOP-UKCCSG-PNET3/HIT-SIOP-PNET4 clinical trials. Contemporary molecular profiling integrating methylation/WCA subtypes and next-generation sequencing was performed. Survival modelling was carried out with patients >3 years old who received craniospinal irradiation (n=336). Association analysis confirmed relationships between methylation and WCA subtypes. Subtypes VI and VII were enriched for WCA-FR ($p<0.0001$) and aneuploidy, whereas subtype VIII was defined solely by i17q ($p<0.0001$). Whilst we observed an overall low mutational burden, WCA-HR harboured recurrent mutations in genes involved in chromatin remodelling ($p=0.007$). No gene-specific events were associated with disease risk, however integration of both methylation subtype and WCA groups enabled improved risk-stratification survival models that outperformed current schemes. The optimal MB_{Grp4}-specific model stratified patients into: favourable-risk (local disease, subtype VII or subtype VI with WCA-FR; 39/194 [20%], 97% 5-year PFS), very-high-risk (metastatic disease with WCA-HR; 71/194 [37%], 50% 5-year PFS) and high-risk (remaining patients; 84/194 [43%], 67% 5-year PFS). Findings were validated in independent cohorts. Comprehensive clinico-molecular assessment of MB_{Grp4} provides important understanding of its clinical and biological heterogeneity. Our novel MB_{Grp4} stratification scheme removes standard risk disease and identifies a favourable risk group (20% of MB_{Grp4}) with potential for therapy de-escalation. Current therapeutic strategies are insufficient for the very-high risk group (encompassing 37% of MB_{Grp4}), for whom novel therapies are urgently required.

MEDB-72. MOLECULAR CHARACTERIZATION OF MEDULLOBLASTOMAS IN A SINGLE INSTITUTION

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INTRODUCTION: The four molecular groups (WNT, SHH, Group 3 and Group 4) in medulloblastoma have been well established for the past decade. New subgroups within the four principal molecular groups have recently been discovered and recognized by WHO classification of Central Nervous System Tumours (5th edition). Subgroups were reported to have distinct somatic copy-number aberrations and clinical outcomes. This further classification could be helpful to refine prognostication and potentially provide risk stratification for treatment planning. AIM: To interrogate archival medulloblastoma samples using Oncoscan Microarray Assay, correlate with clinical features and consider the assay for clinical use. METHODS: Thirty-one archival samples with histological diagnosis of medulloblastoma and molecular grouping results from NanoString were retrieved and evaluated with Oncoscan Microarray Assay. Twenty-six were subjected to DNA methylation profiling to compare the results. Eight cases also had molecular data from next-generation sequencing (NGS) done with the in-house Ampliseq Childhood Cancer Panel. Correlation was made with clinical characteristics and outcomes of these 31 patients. RESULTS: OncoScan microarray showed distinct differences in the copy number profiles of the 31 medulloblastoma samples. Seventeen samples could be further classified into one of 12 subgroups. However, further subgrouping was challenging without first determining the main molecular group especially amongst non-WNT/SHH tumours. DNA methylation results provided corroboration with the Oncoscan subgrouping results in 25 of 26 samples. NGS panel detected additional genetic alterations in 5 of 8 samples. CONCLUSIONS: Oncoscan Microarray Assay showed potential in providing additional molecular information for further subgrouping of medulloblastoma, but was insufficient for determining the main molecular groups. Moving forward, molecular characterization could instead be done through use of NGS panel and DNA methylation, which provides tumour epigenetic profiling on top of copy number variants. These could be used alongside the NanoString platform, which is performed routinely for all medulloblastomas at our centre.

MEDB-73. LIPID METABOLISM AS A THERAPEUTIC VULNERABILITY IN BET INHIBITOR-RESISTANT MEDULLOBLASTOMA

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MYC-driven medulloblastomas are a particularly devastating group of pediatric brain tumors that exhibit resistance and continued progression despite standard of care treatments. Our preclinical work identified BET-bromodomain inhibitors as a potentially promising new class of drugs for children with medulloblastoma and other MYC-driven cancers, providing rationale to evaluate these agents in clinical trials. However, treatment with BET inhibitor (BETi) alone is unlikely to be sufficient to cure, with most tumors evolving to acquire resistance to single-agent targeted therapies. We applied an integrative genomics approach to identify genes and pathways mediating BETi response in medulloblastoma. These studies revealed that MYC-driven medulloblastoma cells with acquired resistance to BETi reinstate transcription of essential genes suppressed by drug and exhibit changes in cell state and new vulnerabilities not present in drug-sensitive cells. We now have a growing body of evidence showing that BET inhibition downregulates the expression of key lipid metabolism genes and metabolism-related signaling pathways, and that medulloblastoma cells with adaptive resistance to drug differentially express and exhibit preferential dependency on specific lipid metabolic genes and transcriptional regulators. Our studies explore the possibility of exploiting these metabolic vulnerabilities to overcome BETi resistance and provide a more efficacious upfront therapy.

MEDB-74. SERIAL ASSESSMENT OF MEASURABLE RESIDUAL DISEASE IN MEDULLOBLASTOMA LIQUID BIOPSIES

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