TUMOR BIOLOGY (NOT FITTING A SPECIFIC DISEASE CATEGORY)

TBIO-01. MUTATION PROFILING OF PAEDIATRIC SOLID TUMOURS IN A COHORT OF SOUTH AFRICAN PATIENTS

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BACKGROUND: The incidence of childhood cancer incidence is increasing gradually in low-middle income countries, such as South Africa. Globally, there is an extensive range of familial- and hereditary-cancer syndromes, where underlying germline variants increase the likelihood of developing cancer in childhood. Next-Generation Sequencing (NGS) technologies have been key in determining the occurrence and genetic contribution of germline variants to paediatric cancer development. We aimed to design and evaluate a candidate gene panel, specific to inherited cancer-predisposing genes to provide a comprehensive insight into the contribution of germline variants to childhood cancer. METHODS: 32 paediatric patients (aged 0-18 years) diagnosed with a malignant tumour were recruited and biological samples were obtained. After quality control, DNA was sequenced using an ion Ampliseq 50 candidate gene panel design and Ion Torrent S5 technologies. Sequencing variants were called using Ion Torrent Suite software and were subsequently annotated using Ion Reporter and Ensembl's VEP. High priority variants were manually analysed using tools such as MutationTaster, SIFT-INDEL and VarSome. Putative identified candidates were validated via Sanger Sequencing. RESULTS: The patients studied had a variety of cancers, the most common being nephroblastoma (13), followed by osteosarcoma (4) and astrocytoma (3). We identified 10 pathogenic / likely pathogenic variants in 10 patients, most of which were novel. CONCLUSIONS: According to literature, we expected ~10% of our patient population to harbour pathogenic or likely pathogenic germline variants, however we reported about 3 times (~30%) more than we expected. Majority of the identified variants are novel; this may be because this is the first study of its kind in an understudied South African population

TBIO-02. MAPPING THE ORIGINS OF PEDIATRIC BRAIN TUMORS TO CELL TYPE LINEAGES IN THE DEVELOPING CEREBELLUM.

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Understanding the cellular origins of cerebellar tumors at single cell resolution may help identify novel therapeutic vulnerabilities to overcome current impediments in pediatric neuro-oncology. One approach to answer this important question involves the mapping of tumor profiles onto normal embryonal central nervous system development. Previous attempts in this regard focused on integrating human tumor data with developing mouse cerebellum atlases, however, these approaches were inherently limited due to species-specific differences. In order to address this critical issue, we use a high resolution developing human cerebellum single cell atlas in order to compare to extended bulk and single cell transcriptomes profiles from pediatric solid tumors. In result, we provide novel and confirmatory findings for the cellular association of medulloblastoma SHH, Group3 and Group4 as well as pilocytic astrocytoma, using comprehensive approaches to decipher the cellular composition and map the origins of childhood brain tumors. We also shed light on the cellular origins of posterior fossa ependymoma and radiation-induced glioma (secondary tumor, occurring after medulloblastoma). As a common feature among the tumor similarity to normal cell types, we identify gradients of differentiation, starting from early progenitor cells to more differentiated cell states, observed in all cerebellar tumor entities investigated at single cell level; thus reflecting possible lineages of origin. Pertaining to clinical application, we identified specific developmental genes shared between cerebellar lineages and associated tumors, and tumor-specific genes absent in all cerebellar lineages. These two categories of genes comprise candidate lineage markers for faithful modeling and, if absent from other organ systems after birth, could become an important source of potential therapeutic targets. Importantly, all analysis results are publicly available via an interactive online user interface (brain-match.org) that serves as an open valuable resource for the scientific community.

TBIO-03. ANGIOGENESIS IN PITUITARY ADENOMA

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The role of angiogenesis in pituitary tumor development used to be questioned, since pituitary tumors have been usually found to be less vascularized than the normal pituitary tissue. Nevertheless, a significantly higher degree of vasculature has been shown in invasive or macropituitary prolactinomas when compared to nonin- vasive and microprolactinomas. We should know VEGF was found firstly in pituitary anterior lobe, then tumor angiogenesis must occur. Meanwhile the vascular arrange- ment raised by VEGF is irregular, that sometimes lead to pituitary apoplexy. In this chapter, hypoxia inducible factors (HIF), transcription factors regulating expression of several genes related to oxygen homeostasis are in response to hypoxic stress. We focus on tumor angiogenesis regulated by the signaling cascade in tumor angiogenesis in pituitary tumor.

TBIO-04. COMPREHENSIVE ANALYSIS OF MUTATIONAL SIGNATURES IN PEDIATRIC CANCERS

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Analysis of mutational signatures can reveal the underlying molecular processes that have caused the somatic mutations found in genomes. We performed an extensive analysis encompassing mutational signatures of single base substitution and, for the first time, signatures of small insertions/deletions in ~800 whole-genome-sequenced tumor-normal pairs from 25 molecularly defined pediatric cancer types. More than half of this cohort consists of pediatric CNS-tumors (n=416), including high- and low-grade gliomas, ependymomas, and embryonal tumors. These were subsequently compared with COSMIC v.3 signatures to identify overlap with the latest set of known mutational signatures. We identified only a small number of mutational signatures active in pediatric cancers when compared to previously analyzed adult cancers. Amongst these, SBS1 and SBS5 were present in nearly all pediatric tumors analyzed, with a significant correlation of signature activity with age at diagnosis, as expected. Further, we found SBS21 activity in a fraction of high-grade gliomas, which is the result of defective DNA mismatch repair, SBS36 in fractions of ETMR and Group4-medulloblastoma, the result of defective base excision repair, and SBS44 in Group4-medulloblastomas, caused by defective DNA mismatch repair. For these signatures, no consistent genetic alteration was identified. We report a significantly smaller proportion of pediatric tumors which show homologous-recombination repair defect signature SBS3 compared to previously published analyses. Additionally, the previous mutational signature analysis of this cohort based on COSMIC v.2 reference signatures had identified a novel substitution signature (Signature.P1), active in the brain tumors ATRT and ependymoma. Our updated results suggest that Signature.P1 is not a pediatric specific mutational signature, but a treatment-associated signature identified in a small fraction of brain tumors that were annotated as treatment-naïve. This analysis provides a systematic overview of mutational signatures in pediatric cancers, which is relevant for understanding tumor biology and future research in defining biomarkers for treatment response.

TBIO-05. R-LOOPS IN PEDIATRIC BRAIN TUMORS

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R-loops are structures containing DNA-RNA hybrids and displaced single-stranded DNA, which are widely distributed across genomic regions. The generation and removal of R-loops is dynamically regulated by several factors including helicases and topoisomerases. Previously, we have identified high levels of R-loops associated with genomic instability in Embryonal Tumors with Multilayered Rosettes (ETMR) (Lambo et al. 2019), which is associated with a sensitivity to drugs targeting topoisomerases and DNA repair. However, it is unknown whether there are other pediatric cancers with high levels of R-loops, and whether R-loops in these tumors are also associated with genomic instability and sensitivity to specific treatments.