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Transcriptomic and epigenomic profiling to reveal TIL and microglia functional phenotype and clonality in pediatric brain tumors

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Scientific Abstract:

Brain tumors are the leading cause of cancer-related mortality in children. Despite medical and surgical advances in cancer treatment, a significant proportion of pediatric brain tumors remain incurable and newer treatments are urgently needed. Numerous lines of evidence support a potentially important role for T cell-mediated immunosurveillance of the CNS in mediating protection against cancer. Immunotherapies that boost the anti-tumor responses of T cells have shown promise in many adult cancers, however translation of their clinical success to pediatric tumors is hindered by a lack of understanding of the tumor immune microenviroment within these tumors. The goal of this project is to define the molecular players and mechanisms involved in anti-tumor immune response in pediatric brain tumors. We will undertake an unbiased and comprehensive approach to define transcriptomic and epigenomic profile of purified tumor-infiltrating lymphocytes (TILs), microglia and other immune cell subsets in a well-characterized cohort of pediatric patients with brain tumors. Utilizing state-of-the-art genomic tools such as single-cell RNA sequencing, ATAC-sequencing and histone ChIP-Seq, we will evaluate the TIL functional phenotype, TCR/BCR sequence and clonality in pediatric brain tumors. In addition, similar analysis in tumor-associated microglia and other key immune cell subsets will unravel their co-regulatory relationship and tumor regulatory mechanisms. Integrated bioinformatics analyses of these datasets will reveal novel immune pathways that may be targeted in immunotherapeutic strategies against pediatric brain tumors.

Lay Abstract:

Brain tumors are a leading cause of death among childhood cancers. Significant proportion of these cancers remains incurable despite surgery, chemotherapy and radiation, which are the current standard of care treatments. Besides, there is significant long-term morbidity, impaired functioning and reduced quality of life in survivors following such treatment. Therefore, newer and less toxic treatments are urgently needed for these tumors. Immunotherapy, a treatment that involves harnessing the body's own immune system to eliminate the tumor, has not only been successful in some adult cancers but also has the advantage of being less toxic and having potential for long-term tumor control. Previous studies have shown that children have better survival outcome when their brain tumors harbor immune cells indicating an anti-tumor immune response. However, a complete picture of the type of infiltrating immune cell, its function, what it is directed against and the other factors/cells within the tumor that influence them, are all unknown. It is important to understand this in order to identify new targets for immunotherapy to boost the anti-tumor immune response. We will undertake an unbiased and comprehensive analysis of the immune cells infiltrating pediatric brain tumors using cutting-edge technology including single cell sequencing that helps us to look into each of these cells individually in great detail. This will enable to select out the specific type of immune cell that is best geared to fight the tumor and utilize this information for personalized cancer therapy.