Serial analysis of CSF ctDNA in metastatic mouse models of medulloblastoma to monitor metastasis evolution

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Goal

- Medulloblastoma is the most prevalent malignant pediatric brain cancer
- We have limited understanding of the underlying molecular mechanisms that direct metastases of medulloblastoma
- Current methods to investigate tumors involve surgical resections which are often invasive and impractical for sampling metastatic sites
- Leveraging the accessibility of cerebrospinal fluid (CSF) which circulates in the central nervous system, and knowledge that tumors shed fragmented DNA called circulating tumor DNA (ctDNA) into CSF, we can investigate genetic and epigenetic alterations using a non-invasive approach termed Liquid Biopsy
- Our goal is to garner insight into the representation of genomic and epigenomic alterations in CSF ctDNA in metastatic medulloblastoma based on molecularly faithful murine models

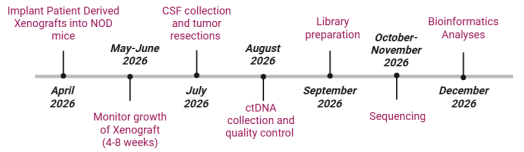
Objectives

1. To establish an NGS-based pipeline, using Enzymatic-Methyl sequencing (EM-seq) that enables methylation-based analysis of low-quantities of ctDNA
2. To apply such EM-seq pipeline on CSF-derived ctDNA from highly metastatic mouse models that recapitulate two of the most aggressive subtypes of MB, MYC driven Group 3 and TP53 mutant SHH MB
3. To corroborate the genomic and epigenomic patterns among CSF-ctDNA, primary tumor, and metastatic tumor specimens in these models

Study Method

Impacts & Outcomes

Project Timeline



Conclusion

References

- Liu APY et al. Serial assessment of measurable residual disease in medulloblastoma liquid biopsies. Cancer Cell. 2021;39(11):1519–1530.e4.
- Hickman RA et al. Real-world experience with circulating tumor DNA in cerebrospinal fluid from patients with central nervous system tumors. Acta Neuropathol Commun. 2024;12:151.
- Brabetz S et al. A biobank of patient-derived pediatric brain tumor models. Nat Med. 2018;24(11):1752–1761.
- Garzia L et al. A hematogenous route for medulloblastoma leptomeningeal metastases. Cell. 2018;172(5):1050–1062.e14.
- Wu X et al. Clonal selection drives genetic divergence of metastatic medulloblastoma. Nature. 2012;482(7386):529–533.