Deciphering 3D Chromatin States Permissive to Driver Alterations in High-Grade Childhood Brain Tumors

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CANCER BIOLOGY

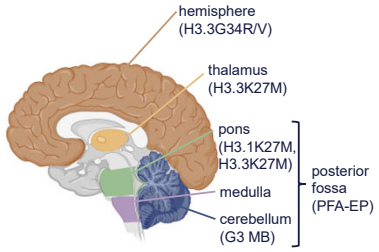
High-grade brain tumors in children are fast-growing and very serious cancers that often appear at a young age. Survival rates are low, and many current treatments were designed for adults, making them less effective for children. Radiation therapy is commonly used, but it can harm a child's brain development, affecting learning and thinking. For these reasons, better knowledge of these tumors is needed to develop safer and more effective treatments for children.

Recent research from our team shows that different types of childhood brain tumors occur at specific ages, in certain parts of the brain, and are linked to particular genetic changes. This suggests that some normal brain cells are more likely than others to become cancerous. We believe this vulnerability may be related to how DNA is folded inside the cell in three dimensions. This DNA structure may keep cells in an immature state that makes them easier to transform into tumor cells. We hypothesize that: (1) there are 3D structures present in glial progenitors that are required for the maintenance of a stem-like state, (2) these 3D structures are transient in the normal brain, but they are permissive to oncogenic transformation, (3) the tumor microenvironment plays a role in the genesis and maintenance of these 3D structures and (4) if these 3D structures were dissolved, the tumor cells would progress towards differentiation and proliferate less.

Main Goal

We will explore the 3D chromatin conformation of pediatric brain tumors, as it has been overlooked in previous studies yet seems to be important for tumor initiation and maintenance. We will focus on

(1) posterior fossa A ependymoma (PFA),
(2) Group 3 medulloblastoma with and without isochromosome 17(G3 MB),
(3) hemispheric H3.3G34R/V high-grade glioma,
(4) pontine H3.1K27M and H3.3K27M high-grade glioma and
(5) thalamic H3.3K27M high-grade glioma.



Our working hypothesis is that these tumors arise in cell types of which the brain location, tumor micro-environment (TME) and 3D chromatin confirmation facilitate the oncogenic transformation once driver mutations are acquired.

Objectives & Impact

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Project Timeline

Project Deliverables by March 2027:

- Demonstrate that the co-option of 3D structures is uniform across all cancer cells in tumors as is the case for K27M-mutant HGG making it realistic to design therapies targeting these structure.
- Identify the developmental windows and chromatin structures that make individuals susceptible to the oncogenic effect of specific genetic alterations in brain tumors. This will impact modeling and screening for early detection/prevention.
- Extend analyses of the 3D genome and epigenome to sarcomas as they share similar cellular/lineage hierarchies.