Understanding the Role of Eed Deletion in Medulloblastoma

Medulloblastoma, the most common malignant pediatric brain cancer, is uniquely sensitive to DNA damage-inducing therapies, with conventional treatment resulting in an 80% 5-year survival rate. Researching the apoptotic pathways that make treatment effective in some tumors and how those pathways contribute to resistance in others may identify therapies that reduce the need for toxic radiation and chemotherapy. In cerebellar development, physiologic Sonic Hedgehog (SHH) signaling drives proliferation of cerebellar granule neuron progenitors (CGNPs). Similarly, pathologic SHH hyperactivation drives proliferation in SHH-subgroup medulloblastoma, which makes up 30% of medulloblastoma cases. SHH signaling upregulates target genes in part by preventing H3K27 trimethylation marks via the JMJD3/KDM6B demethylase complex. In differentiated cerebellar neurons, where SHH signaling is low, the polycomb repressive complex 2 (PRC2) silences SHH target genes by trimethylating H3K27 residues in regulatory regions. Our data show that blocking the PRC2 through genetic deletion has varying effects in different contexts. When the PRC2-component Eed is deleted in SHH-subtype medulloblastomas that form in mice engineered for SHH hyperactivation, the tumors show initially slower growth compared to tumors in Eed-intact controls; however, the mice have significantly poorer survival. Therefore, this study aims to understand the mechanisms of initially reduced tumor growth and ultimately more rapid tumor progression. Our recent single cell gene expression analysis showed that Eed deletion in CGNPs induced genes involved in muscle cell differentiation, including myogenin and troponin. We will characterize Eed-deleted medulloblastoma using fluorescence-activated cell sorting (FACS) as well as immunohistochemistry (IHC). The first aim of this study is to elucidate how cell cycle dynamics are altered in Eed-deleted medulloblastomas. The second aim of the study tests whether Eed deletion alters the levels of cell cycle markers, cell death, and aberrant expression of muscular proteins in SHH-driven medulloblastoma. Our cell cycle studies show that Eed deletion slows tumor growth in early development, but the tumor later develops EED independence, resulting in more rapid progression and decreased survival. Additionally, our data show that Eed deletion alters the expression of proteins related to proliferation, differentiation, apoptosis, and muscle development.