Defining Epigenetic Drivers of Medulloblastoma – Literature Review & Project Goals

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Medulloblastoma is a malignant neoplasm of undifferentiated cells arising from specific types of neural stem/ progenitor cells in the hindbrain (1, 2). These neoplasms typically arise from the cerebellar vermis (3), disproportionally occur in infants and young children of ages 1-4, and have the highest incidence of all childhood malignancies (4-6). Originally, medulloblastoma was characterized by its histology, but advances in genetics allowed researchers to analyze the genomes and transcriptomes of medulloblastoma tissues. These analyses determined that the disease broadly falls into one of four molecular subgroups (6-11): WNT, SHH, Group 3, and Group 4.

The WNT subgroup is characterized by lack of metastasis, loss of chromosome 6, and mutations in CTNNB1, which lead to aberrant WNT growth pathway signaling (6). They have an excellent prognosis, with a five-year survival rate of 95% (9). WMT medulloblastoma is thought to arise from the progenitor cells of the lower rhombic lip (12).

The SHH subgroup is characterized by mutations in PTCH1, SMO, or SUFU, regulators of the SHH growth pathway, leading to aberrant SHH signaling. Other aberrations in this subgroup include overexpression of MYCN and GLI2, p53 mutation, and chromosomal aberrations including gain of chromosome 3q, and loss of 9q and 10q (6). Like WNT, SHH tumors rarely metastasize, and they tend to have intermediate to good prognoses, with a five-year survival rate of 60-80% (6, 9). SHH medulloblastoma arises from the granule precursor neurons (2, 13).

Group 3 tumors differ from WNT and SHH in that they more commonly arise in males over females, metastasis is very common, and they have worse prognoses than the former two groups (6). Group 3 tumors are characterized by frequent MYC amplification, gain of chromosomes 1q, 17q, 18q, and 7, loss of chromosome 5q, 10q, 11p, 16q, and 8, and have a dismal five-year survival rate of only 50% (6, 9). It is not known what the cell of origin for Group 3 medulloblastomas is (14), however Purkinje cell progenitor cells are one possibility (15).

Group 4 tumors are the most common of all subgroups, and share a higher incidence in males than females along with Group 3 tumors. They also present with a higher incidence of metastasis than WNT or SHH subgroups (6, 9). They are characterized by frequent MYCN and CDK6 amplification, gain of chromosomes 17q, 18q, and 7, loss of chromosomes 11p, 8, and X, and

isochromosome 17q (6). Group 4 medulloblastomas are associated with an intermediate five-year survival of 60% (9), and are thought to arise from precursor cells in the upper rhombic lip (14).

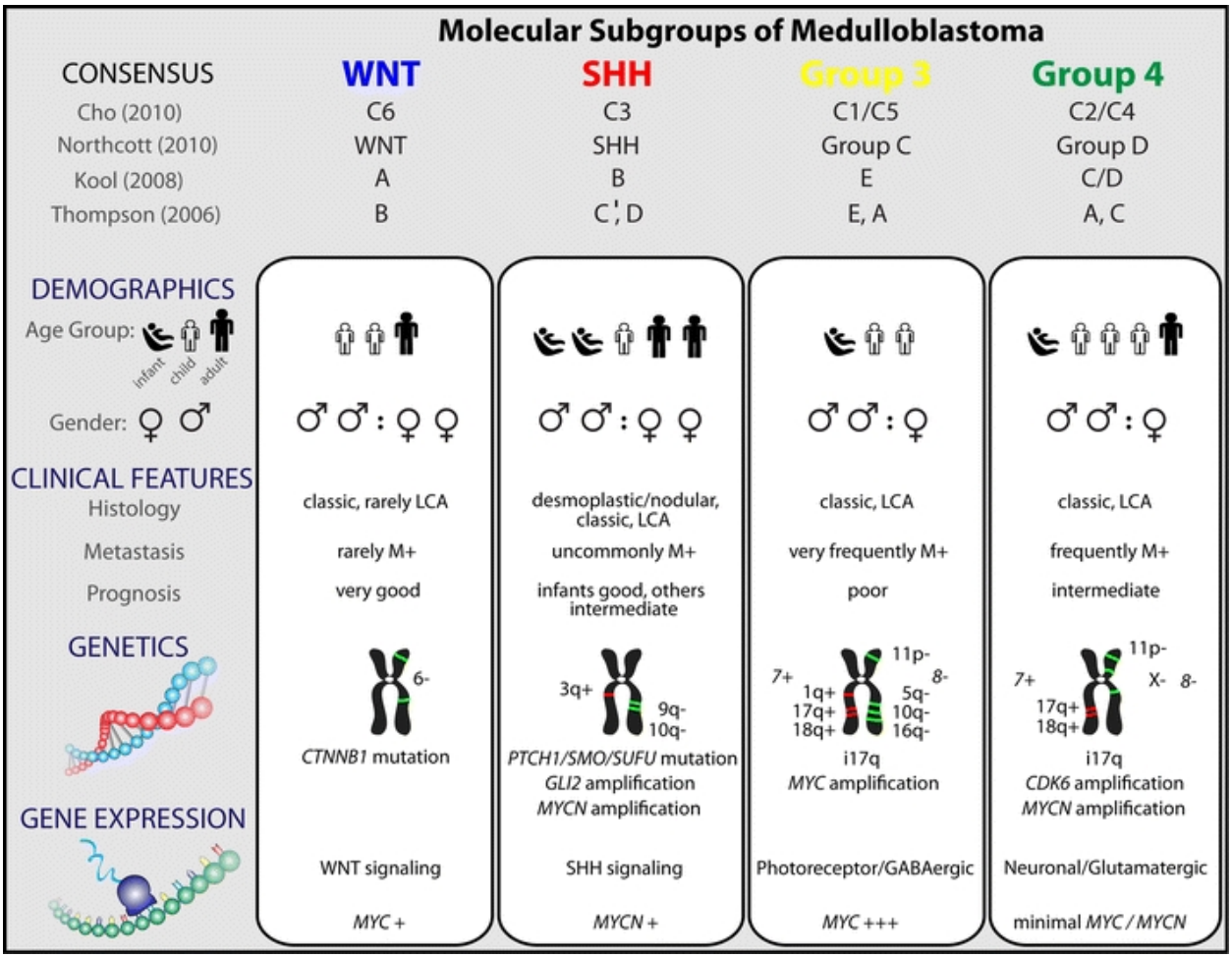
Treatment for medulloblastoma involves gross surgical resection (16), followed by irradiation of the entire cranio-spinal axis (16-18), and broad-range chemotherapy including regimens of cisplatin/carboplatin, vincristine, and cyclophosphamide (16, 19, 20). Due to sustaining intensive irradiation during childhood, developmental sequelae are severe and these include neurocognitive defects, postoperative mutism, endocrinopathies, sterility, and risk of secondary neoplasms including high grade glioblastoma, and meningioma (17, 20). Since side-effects of current treatment impact quality of life, and five-year survival remains low in Group 3 tumors, it is necessary to develop targeted therapies with reduced side effects.

One example of targeted therapy in SHH medulloblastoma is the SMO inhibitor vismodegib (21). This inhibitor blocks SHH signaling by preventing SMO from interacting with GLI2, and is effective in treating some SHH tumors that contain mutations in PTCH1 (the tumor suppressor that negatively regulates SMO) (22). Despite containing many chromosomal abnormalities, and overexpression of growth transcription factors MYC and MYCN, Group 3 and Group 4 medulloblastomas lack known mutation drivers (19) (such as CTNNB1 in WNT, or PTCH1 in SHH) that enable specific growth pathways, and provide targets to exploit (7). Lack of known mutational drivers to treat Group 3 and 4 tumors presents a challenge in finding targeted therapy options.

Group 3 and 4 tumors share a high incidence of alterations in epigenetic regulators (19). Epigenetics is an umbrella term for multiple cellular processes that control gene expression without any change in the genomic sequence (19, 23). These mechanisms are heritable from parent to daughter cells, and determine the expression pattern of genes within cells, being responsible for cell differentiation and development (19, 24). Aberrations in epigenetic regulation can give rise to malignant neoplasms (24). These mechanisms include DNA methylation, histone modifications and chromatin remodeling, microRNA silencing, and noncoding-RNA silencing (19). Methylation of DNA can repress gene transcription, silencing specific genes that would otherwise be expressed. Histone modifications determine the conformational state of the DNA/histone complexes responsible for chromatin configuration. For gene transcription to occur, histones must unravel DNA/histone complexes to allow access of the transcriptional machinery (25). Epigenetic alterations in medulloblastoma include hypermethylation of the tumor suppressor genes expressing

p16 and MLH1, aberrations in H3K27 and H3K6 methylation, and somatic mutations in histone modifiers including acetyltransferases, deacetylases, lysine methyltransferases, demethylases, and members of the polycomb transcriptional repressor complex (19, 24). Since these regulators are commonly aberrant in Group 3 and 4 tumors, they present an attractive group for studying and developing targeted therapies.

My project involves epigenetic screening of cells from Group 3 medulloblastoma. Many cell lines have been derived from this group including D425, D458, D283, and Med8A (26). Since primary cell lines, and patient tissue samples are very difficult to grow in vitro, this project will focus on screening the cell lines that do easily grow. From this work, I aim to find specific targets that can be exploited in the treatment of Group 3 medulloblastoma.



Summary of the four major molecular subgroups of medulloblastoma (6).

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