

SCIENTIFIC PAPERS

1. Traditional and Electronic Ki-67 Quantitation in Oligodendrogliomas

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The Ki-67 proliferative index has become a useful, objective, immunohistochemical tool that can aid in grading and prognostication for patients with oligodendrogliomas. Previous studies have described the prognostic significance of the Ki-67 index for such patients.

According to the WHO classification of tumors of the central nervous system (2007) "mitotic activity is low in WHO grade II oligodendroglioma, and labeling indices for proliferation markers are accordingly low, usually below 5%". Furthermore, the predictive value of the Ki-67 index appears to be independent of age, tumor site, and histological grade. What is less well described is the relative accuracy of traditional vs. semi-automated methods of enumeration for a test where small differences can influence grading, prognosis and treatment. Tang et al. (2012), studying gastroenteropancreatic neuroendocrine tumours, found high concordance between two semi-automated methods for Ki-67 quantitation whereas "eyeballed estimates" were far less reliable. We will compare the reported proliferative index estimates to those calculated by digital image analysis of 35 recent oligodendrogliomas from the LHSC Pathology archives.

2. SUMO1-CDK6 conjugation drives the cell cycle and retains the self renewal of glioblastoma stem cells

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The current concept in the cell cycle stipulates that constant synthesis without coupled ubiquitin-mediated proteolysis maintains the levels of cyclin-dependent kinase proteins through the cell cycle. CDK proteins are elevated in glioblastoma, which has long been thought due to gene amplifications, although the amplifications occur only in a small set of the tumors according to the genome.

In this study, we show that the G1 phase CDK6 is a substrate of both ubiquitin and small ubiquitin-like modifier-1 (SUMO1), and that CDK6 is sumoylated due to the elevated activity of SUMO1 conjugation in glioblastoma. CDK6 sumoylation at Lys 216 structurally blocks the access of ubiquitination molecules to the Lys 147 ubiquitination site; thus, CDK6 sumoylation stabilize the protein, maintains the kinase activity and drives the cell cycle through G1/S transition. Inhibition of SUMO1 conjugation causes G1 arrest and abolishes the self-renewal and tumorigenic property of glioblastoma initiating or stem cells. In conclusion, SUMO1-CDK6 conjugation constitutes a new mechanism of cell cycle control and selective inhibition of SUMO1 conjugation may provide a novel strategy for the development of the cancer stem cells-targeted treatment.

3. Characteristics of Glioblastoma in Latino Americans

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Latino Americans are a rapidly growing ethnic group in the United States. The characteristics of glioblastoma in this population is poorly studied. We have evaluated the data of 47,540 glioblastoma patients from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute. This SEER data from 1973-2000 includes up to 13 cancer registries. For 2001 to 2011, the data has improved geographic coverage with 18 registries encompassing 28% of the U.S. population.

Latinos have a lower incidence of GBM than non-Latino Whites. Gender distribution is similar. The total SEER data show that Latinos present slightly younger and have a higher incidence of giant cell glioblastoma and gliosarcoma than non-Latino Whites. Despite higher rates of radiation therapy, the one year survival rate (34.7%) for non-Latino White populations is less than for Latinos (39.0%, $p < 0.001$). Subset analyses (2001-2011) of all the above parameters show similar results except for gliosarcoma incidence. A literature search does not identify MGMT or IDH1 data regarding Latino Americans.

We have assessed 2 prognostic markers in 30 Latino glioblastoma patients. MGMT methylation is present in 24% and IDH1 mutation is found in 12.5%. Our preliminary data suggests that Latinos may have a greater incidence of MGMT unmethylated tumors. Younger age may possibly contribute to improved survival in Latinos but the underlying molecular basis is unresolved.

4. "Biphasic" histology is associated with the non-WNT/SHH molecular subtype of medulloblastoma

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Introduction: In 2007, Ellison et al coined the term "biphasic" medulloblastoma (B-MB) to characterize histology that mimicked the desmoplastic nodular (DN) variant on routine staining, but which lacked internodular reticulin deposition. Via interphase FISH, and utilizing markers for 9q22 and chromosome 17 alterations (ie, -17p and i17q), Ellison et al. suggested that B-MB and DN-MB were genetically different.

Methods: We performed a clinicopathologic review of MBs treated at BCCH from 1986-2011. Using nanoString's nCounter Analysis System (nCAS), each tumor was molecularly subtyped (ie, WNT, SHH, group 3 or group 4). All original glass slides were reviewed to determine WHO histologic subtype [ie, classic, large cell anaplastic (LCA), DN, MB with extensive nodularity (MBEN)]. Tumors were also evaluated for nodularity (scattered vs. frequent) and advanced neuronal differentiation. Reticulin staining was assessed on all cases.