Glioblastomas are the most frequent and aggressive primary brain tumor in adults and despite recent therapeutic advances, they are resistant to treatment. Increasing malignancy of gliomas correlates with an increase in cellularity and a poorly organized tumor vasculature, leading to insufficient blood supply, hypoxic areas, and ultimately to the formation of necrosis. Hypoxia induces direct or indirect changes in the biology of solid tumor and their microenvironment through the activation of HIF transcription factors, leading to increased aggressiveness and tumor resistance to therapy. Not much is known about the epigenetic alterations induced by hypoxia and how they could alter tumor biology.

In the present study, we have utilized PIMO as a specific marker of hypoxia in glioblastoma patients treated with PIMO preoperatively. We have estimated PIMO positivity in each tumor (5-45%) and determined that it positively correlates with the hypoxia marker CA IX (r=0.57). In addition, 10 surgical PIMO cases were dissociated, immune labeled using PIMO antibody, followed by DNA isolation and methylation profiling. Our analysis of differentially top 4000 differentially methylated probes suggests that PIMO-positive (hypoxic) cells are differentially methylated compared to the PIMO-negative cells and these changes are associated with genes involved in hypoxic cellular response. We will validate these findings in additional glioblastoma cases and assess the mechanism of these epigenetic alterations in vitro in glioma stem cell culture conditions and upon exposure of the cells hypoxic conditions.

Molecular characterization of pediatric low-grade glioma (pLGG) over the last decade has identified recurrent alterations, most commonly involving BRAF, and less frequently other pathways including MYB and MYBL1. Many of these molecular markers have been exploited clinically to aid in diagnosis and treatment decisions. However, their frequency and prognostic significance remain unknown. Further, a significant portion of cases do not have any of these alterations and what underlies these cases remains unknown. To address this we compiled a cohort of 562 patients diagnosed at SickKids from 1990-2017. We identified molecular alterations in 454 cases (81% of the cohort). The most frequent events were those involving BRAF; either as fusions (most commonly with KIAA1549 (30%)) or V600E mutations (17%) and NF-1 (22%). Less frequently, we identified recurrent FGFR1 fusions and mutations (3%), MYB/MYBL1 alterations (2%), H3F3AK27M (2%) or IDH1R132H (0.5%) mutations, as well as other novel rare events. Survival analysis revealed significantly better progression-free survival (PFS) and overall survival (OS) of KIAA1549-BRAF fused patients compared to B RAFV600E with 10-year OS 97.7% (95%, CI 95.5-100) and 83.9% (95%, CI 72.5-95.6), respectively. In addition to survival, molecular alterations predicted differences in response to conventional therapeutics; BRAF fused patients showed a 46% response-rate, versus only 14% in V600E patients. pLGGs harboring H3F3AK27M progressed early with median PFS of 11 months. In patients with MYB/MYBL1, FGFR1/FGFR2 alterations, we observed only one death (FGFR1N546K case). The work here represents the largest cohort of pLGGs with molecular profiling and their impact on the clinical behaviour of the disease.

The genetic landscape of pediatric low-grade gliomas: Incidence, prognosis and response to therapy - a SickKids pLGG Task Force update


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Molecular characterization of pediatric low-grade glioma (pLGG) over the last decade has identified recurrent alterations, most commonly involving BRAF, and less frequently other pathways including MYB and MYBL1. Many of these molecular markers have been exploited clinically to aid in diagnosis and treatment decisions. However, their frequency and prognostic significance remain unknown. Further, a significant portion of cases do not have any of these alterations and what underlies these cases remains unknown. To address this we compiled a cohort of 562 patients diagnosed at SickKids from 1990-2017. We identified molecular alterations in 454 cases (81% of the cohort). The most frequent events were those involving BRAF; either as fusions (most commonly with KIAA1549 (30%)) or V600E mutations (17%) and NF-1 (22%). Less frequently, we identified recurrent FGFR1 fusions and mutations (3%), MYB/MYBL1 alterations (2%), H3F3AK27M (2%) or IDH1R132H (0.5%) mutations, as well as other novel rare events. Survival analysis revealed significantly better progression-free survival (PFS) and overall survival (OS) of KIAA1549-BRAF fused patients compared to BRAFV600E with 10-year OS 97.7% (95%, CI 95.5-100) and 83.9% (95%, CI 72.5-95.6), respectively. In addition to survival, molecular alterations predicted differences in response to conventional therapeutics; BRAF fused patients showed a 46% response-rate, versus only 14% in V600E patients. pLGGs harboring H3F3AK27M progressed early with median PFS of 11 months. In patients with MYB/MYBL1, FGFR1/FGFR2 alterations, we observed only one death (FGFR1N546K case). The work here represents the largest cohort of pLGGs with molecular profiling and their impact on the clinical behaviour of the disease.

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Altering in the epigenetic profile of glioblastoma tumors within hypoxic tumor regions

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Glioblastomas are the most frequent and aggressive primary brain tumor in adults and despite recent therapeutic advances, they are resistant to treatment. Increasing malignancy of gliomas correlates with an increase in cellularity and a poorly organized tumor vasculature, leading to insufficient blood supply, hypoxic areas, and ultimately to the formation of necrosis. Hypoxia induces direct or indirect changes in the biology of solid tumor and their microenvironment through the activation of HIF transcription factors, leading to increased aggressiveness and tumor resistance to therapy. Not much is known about the epigenetic alterations induced by hypoxia and how they could alter tumor biology.

In the present study, we have utilized PIMO as a specific marker of hypoxia in glioblastoma patients treated with PIMO preoperatively. We have estimated PIMO positivity in each tumor (5-45%) and determined that it positively correlates with the hypoxia marker CA IX (r=0.57). In addition, 10 surgical PIMO cases were dissociated, immune labeled using PIMO antibody, followed by DNA isolation and methylation profiling. Our analysis of differentially top 4000 differentially methylated probes suggests that PIMO-positive (hypoxic) cells are differentially methylated compared to the PIMO-negative cells and these changes are associated with genes involved in hypoxic cellular response. We will validate these findings in additional glioblastoma cases and assess the mechanism of these epigenetic alterations in vitro in glioma stem cell culture conditions and upon exposure of the cells hypoxic conditions.

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CD271/p75NTR is a novel diagnostic marker, prognostic indicator and therapeutic target for SHH medulloblastoma

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The extensive heterogeneity both between and within the medulloblastoma (MB) subgroups underscores a critical need for variant-specific biomarkers and therapeutic strategies. We
Intracranial growing teratoma syndrome (IGTS): An international retrospective study


BACKGROUND: IGTS is a rare phenomenon of paradoxical germ cell tumor (GCT) growth during or following treatment despite normalization of tumor markers. We sought to evaluate the frequency, clinical characteristics and outcome of IGTS in patients in 21 North-American and Australian institutions. METHODS: Patients with IGTS diagnosed from 2000-2017 were retrospectively evaluated. RESULTS: Out of 739 GCT diagnoses, IGTS was identified in 33 patients (4.5%). IGTS occurred in 9/191 (4.7%) mixed-malignant GCTs, 4/22 (18.2%) immature teratomas (ITs), 3/472 (0.6%) germinomas/germinomas with mature teratoma, and in 17 secreting non-biopsied tumours. Median age at GCT diagnosis was 10.9 years (range 1.8-19.4). Male gender (84%) and pineal location (88%) predominated. Of 27 patients with elevated markers, median serum AFP and Beta-HCG were 70 ng/mL (range 9.2-932) and 44 IU/L (range 4.2-493), respectively. IGTS occurred at a median time of 2 months (range 0.5-32) from diagnosis, during chemotherapy in 85%, radiation in 3%, and after treatment completion in 12%. Surgical resection was attempted in all, leading to gross total resection in 76%. Most patients (79%) resumed GCT chemotherapy/radiation after surgery. At a median follow-up of 5.3 years (range 0.3-12), all but 2 patients are alive (1 succumbed to progressive disease, 1 to malignant transformation of GCT). CONCLUSION: IGTS occurred in less than 5% of patients with GCT and most commonly after initiation of chemotherapy. IGTS was more common in patients with IT-only on biopsy than with mixed-malignant GCT. Surgical resection is a principal treatment modality. Survival outcomes for patients who developed IGTS are favourable.