Gliomas are among the deadliest cancers, with median survivals varying between months for the malignant grade IV glioblastoma (GBM), to decades for low-grade glioma (LGG). Gliomas progress by brain tissue invasion. The aim of our Laboratory is to understand mechanisms underlying glioma invasion. This involves the identification of biomarkers, genetic regulators, signaling networks and molecular effectors of invasion that can ultimately be targeted to control glioma progression. Through an active exchange between clinicians and our laboratory, we are collecting freshly resected glioma biopsies for genotyping and ex vivo cell culture. In parallel, we are entering personal, clinical, imaging, histopathological and molecular annotations to construct a comprehensive glioma patient database. This information is useful for classifying gliomas into molecular subsets and allowing identification of biomarkers that may reveal novel glioma pathways.

**IDM mutations in low-grade gliomas**

IDM neomorphic mutation (IDHmut), found in 80% LGG, catalyzes a α-ketoglutarate conversion into 2-hydroxylglutarate, accumulation of which maintains CpG methylation. This results in MGMT epigenetic silencing and TP53 CpG-to-CpA mutation- al transition. We stratified 210 LGG according to these molecular criteria in a retrospective study. Although IDHmut status is associated with a lower risk of death (HRdeath=0.35, P=0.0023), IDHmut subsets consistently showed higher risks of malignant transformation (MT) than of death. This supports the finding that molecular events relevant to IDM mutation impacts early glioma development prior to MT (see Leu et al., 2016).

The interplay of 3q26 clustered genes SOX2, PIK3CA, MIFN1 and OPAL in GBM cell invasion

Chromosome band 3q26, frequently altered in GBM, contains the genes for transcription factor SOX2, growth factor/AKT signaling activator PIK3CA, and MIFN1 and OPAL, two effectors of mitochondria fusion, a process linked to inhibition of cell motility (Fig. 1A). We aimed at determining the roles of these four genes in GBM cell invasion. Compared to parental LN319 GBM cells, individual 3q26 gene knock-downs consistently abrogated mitochondria, and enhanced cell invasion (Fig. 1B.C). These phenotype similarities suggested that these 3q26 genes act on a common invasion pathway. Pharmacological inactivation of AKT, downstream of PIK3CA, impairs SOX2 nuclear localization and aggravates SOX2 turn-over (Fig. 2A). Chromatin-immunoprecipitation and luciferase reporter gene assays show that SOX2 trans-activates PIK3CA, MIFN1 and OPAL (Fig. 2B.C). This indicates a positive regulation loop where AKT signaling activates SOX2 function, which in turn activates PIK3CA, MIFN1 and OPAL transcription. Copy number variations at 3q26 analyzed in 100 glioma biopsies show frequent SOX2 gain (29%) and OPAL loss (32%) (Fig. 3A). SOX2 amplification is consistent with enhanced transcriptional activation of oncogenic targets such as PIK3CA. In contrast, OPAL needs to be lost to counter-act the impact of SOX2 on mitochondria fusion and invasion suppression. Thus, among the genes trans-activated by SOX2, are oncogenic and tumor suppressor genes. While the oncogenic ones (PIK3CA) are kept ‘on’, OPAL may need to be turned ‘off’ by deletion. Thus, we provide evidence that a regional interplay between 3q26 genes promotes glioma invasion (Fig. 3B). Copy number variations of 3q26 genes suggest optimization of these oncogenic activities and are currently being tested for their impact on tumor invasion in glioma patients (see connection to clinical practice).

**Combined expression of nestin and SPARC identifies isolated astrocytoma cells in brain tissue**

Identification of individual invasive glioma cells in brain tissue requires markers that specifically recognize tumor cells. We tested the presence of proteins involved in glioma development (proliferation, survival, invasion, differentiation, transcription and metabolism) on a tissue micro-array that contains brain sections at various distances from the tumor core and various glioma history and grade. Glial progenitor marker nestin together with secreted acidic and rich in cysteine (SPARC) represent a specific combination for recognizing glioma cells in a non-neoplastic environment (see Aljammal et al., 2015).

**Selected Publications**


**Group Members**

PD Dr. Jean-Louis Boulay (Project Leader)
Mrs. Silvia Fabbi (Master Student)
Mrs. Archana Ramadoss* (PhD Student)
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*Left during report period

**Brain Tumor Biology**