are able to specifically block glioblastoma invasion in vitro and in vivo, where they also prolong survival in glioblastoma animal models. To better understand the functions of GSK-3 in glioblastoma we used proteomics which revealed major changes in cytoskeletal proteins, with downregulation of the EMT marker vimentin being the most significant alteration. Vimentin is an intermediate filament protein that functions as an organizer of a number of critical proteins involved in attachment, migration, and cell signaling. The downregulation of vimentin was rapid and due to alterations in its dynamics in response to GSK-3 inhibition. GSK-3 and vimentin were shown to associate with each other in glioblastoma cells, and reduction in vimentin phosphorylation was observed suggesting it may be a novel substrate of GSK-3. We showed that vimentin is highly expressed in patient glioblastoma samples and higher levels of vimentin are associated with poorer prognosis. Vimentin knockdown also reduced glioblastoma cell migration. The mechanism of action of GSK-3 inhibition in the context of glioblastoma invasion and the potential of developing a therapeutic strategy based on these observations will be discussed.

S4 - Session1 1015-1030

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Bone marrow derived immune cells and their role in tumor heterogeneity

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The role of bone marrow derived cells (BMDC) in tumor neo-vascularization remains controversial. We previously demonstrated recruitment and migration of distinct subpopulations of BMDCs to Glioblastoma Multiforme (GBM), and association with the GBM vasculature in a highly tumor region dependent manner. Continuation of this work has focused on establishing the molecular alterations generated in BMDC as a consequence of interaction with the GBM tumor microenvironment. Our second goal has been to establish whether the tumor microenvironment influences differentiation and contribution of BMDC in GBMs. Intracranial xenograft models were created in chimeric mice generated by reconstituting the bone marrow with fluorescent (gfp or dsred) BM. BMDC were isolated from the GBM microenvironment using FACS sorting of the fluorescent tag at early and late stages of GBM growth, in addition to following treatment with RTx and AATx. We demonstrate that VEGF inhibition though indirect mechanisms, RTx, and direct mechanisms, VEGFTRap, can alter the differential recruitment of pBMDCs observed through normal tumor progression. It is known that inhibition of VEGF leads to an increase in ANG2 signal, which may in turn be linked to the recruitment of pBMDCs. Through addition of an ANG2 inhibitor we can show that through concomitant VEGF and ANG2 inhibition, pBMDC recruitment can be prevented. These results suggest that BMDC contribute through distinct mechanisms to tumor invasion and neo-vascularization and thereby targeting the specific cascade of angiogenic and invasion factors will prevent the pro-tumoral contribution of BMDC in supporting tumor growth and aiding in response to therapy.

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Role of hexokinase 2 (HK2) in modulating tumor metabolism and response to therapy in glioblastoma

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Glioblastoma (GBM), similar to many other cancers, exhibits enhanced aerobic glycolysis with concomitant lactate production, a phenomenon known as the Warburg effect. We have demonstrated that preferential expression of Hexokinase 2 (HK2) is a critical mediator of metabolic reprograming in GBMs and its inhibition is a potential therapeutic strategy for sensitization of GBM tumors to radiation (RAD) and/or temozolomide (TMZ**).** Our results indicate that conditional HK2 inhibition disrupts energy homeostasis and sensitizes GBMs to radiation and chemotherapy. In GBM xenografts, conditional HK2 loss sensitizes GBM tumors to concomitant RAD/TMZ and results in a significant survival benefit in the mice. Moreover, loss of HK2 resulted in GBM remodeling with HK2 knockdowns showing increased necrosis, hypoxia, inflammatory infiltration and reduced vascularization. We demonstrate that targeting a key metabolic enzyme involved in the Warburg effect might improve the efficacy of current therapeutic regimen and provide a unique paradigm for the management of GBMs.

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Classifying medulloblastoma into molecular subgroups: Means, motive, and opportunity

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Current medulloblastoma protocols stratify patients based on clinical features: patient age, metastatic stage, extent of resection, and histological variant. Stark prognostic and genetic differences between the four subgroups suggest that subgroup-specific molecular biomarkers could improve patient prognostication. Method: Molecular biomarkers were identified from a discovery set of 673 medulloblastomas from 43 cities around the globe.