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Comparison of genomic alterations in untreated versus treated glioblastoma

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Glioblastoma (GBM) is a heterogeneous group of tumors despite a uniform histological diagnosis. The varied behavior and response to therapies is associated with the genomic alterations that exist within the tumors. Genomic profiling has been utilized to identify potentially actionable gene alterations in various cancers, including primary brain tumors. We aimed to illustrate that genomic alterations in recurrent GBM are distinct from the primary untreated tumor. Next-generation sequencing was performed on paired specimens from 10 glioblastoma patients. One patient had a second recurrence available for analysis resulting in 21 tumor specimens. We found that the somatic alteration profile differed between primary and recurrent GBM. As the specific alterations are identified and compared, further information will be gleaned about potential actionable alterations and guidance of therapy based upon these alterations.

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Targeting the microenvironment for therapy of primary and metastatic brain tumors

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The median survival of patients with the primary or metastatic brain tumor is limited due to resistance to all standard therapies. The mechanism of pan-resistance against the systemic therapy has been attributed to the blood-brain-barrier and or p-glycoprotein which prevent the drugs from reaching the brain lesions. We have recently reported that activated astrocytes and endothelial cells establish gap-junction communication channel with the tumor cells and protect tumor cells from chemotherapeutic agents by a mechanism involving the phosphorylation of endothelin receptors on tumor cells leading to up-regulation of multiple genes among which are survival or anti-apoptotic genes. We translated in vitro observation into the preclinical in vivo models that nude mice bearing orthotopic human glioblastoma or metastatic human breast or lung cancers in brain were treated by the blockade of the endothelin axis using the dual antagonist, macitentan, combined with taxol or temozolomide. The combination therapy significantly regress the established primary or metastatic brain tumors and prolonged the disease free survival of mice for months after mice in other treatment groups died. Immunohistochemical analysis demonstrated that treatment with macitentan inhibited phosphorylation of the endothelin receptors A and B on tumor cells and tumor-associated endothelial cells. The addition of chemotherapeutic agents produced massive apoptosis in both tumor cells and dividing tumor-associated endothelial cells. Inhibition of endothelin receptor phosphorylation on both tumor cells and tumor-associated endothelial cells inhibits survival pathways in these cells which enhances their sensitivity to chemotherapy. Macitentan plus chemotherapy is well tolerated, produces durable responses and clinical evaluation is ongoing.

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