

arrest and reduced apoptosis. In addition, we recently identified in human stem cells a novel protective role of HMGA2 at replication forks, a function high jacked in cancer (stem) cells. Here, we identified HMGA2 in primary human GB cells and at the migrating front in a mouse model of primary GB. Oncofetal HMGA2 is a new nuclear factor impacting on TMZ resistance. We show that knockdown (kd) of HMGA2 in GB cells increases significantly the sensitivity of GB cells to alkylating agents, as determined by the detection of gamma H2AX nuclear foci, a marker of double DNA breakage, and increased caspase 3/7 activity upon TMZ treatment. We utilized the ability of DNA minor groove binding drugs to compete with HMGA2 for DNA binding and developed a new combinatorial therapeutic strategy that significantly enhanced the ability of TMZ to induce GB cell death.

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A ten-microRNA signature for robust prediction of clinical outcome in glioblastoma

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In this study we investigated the potential of microRNA expression to predict survival in adult glioblastoma. MicroRNA and mRNA expression data were accessed from The Cancer Genome Atlas. LASSO regression models were used to identify a prognostic microRNA signature. Functionally relevant targets of microRNAs were determined using bioinformatic microRNA target prediction, experimental validation and correlation of microRNA and mRNA expression data. A 10-microRNA prognostic signature was identified with a combined risk score strongly associated with overall survival. The signature optimally delineated prognosis groups in the proneural and temozolomide-treated cohorts. The statistical significance of the microRNA signature was at least as effective as MGMT methylation in this dataset. The 10-microRNA risk score was validated in an independent dataset where it also significantly predicted survival in lower grade glioma. The majority of the 10 microRNAs have been previously linked to glioblastoma biology or treatment response. Targets of the signature microRNAs were predicted and expression pattern correlation revealed a number of relevant microRNA/target pairs, which were validated in vitro. We have developed a novel, biologically relevant microRNA signature that stratifies high- and low-risk patients in glioblastoma. MicroRNA/target interactions identified within the signature point to novel regulatory networks and indicate a robust and functionally relevant signature, which may be effective alone or in combination with MGMT methylation.

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The effect of intra-arterial delivery of temozolomide with or without osmotic blood-brain barrier disruption and combined to radiotherapy

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The effect of intra-arterial delivery of temozolomide with or without osmotic blood-brain barrier disruption and combined to radiotherapy Temozolomide (TMZ) is the chemotherapeutic agent used in combination with radiotherapy as part of the standard treatment of glioblastoma. Only 20% of the dose administered orally reaches the cerebrospinal fluid. The intra-arterial (IA) administration of drugs following an osmotic blood-brain barrier disruption (OBBBD) allows a greater delivery of these drugs to the central nervous system (CNS). The IA delivery of TMZ, with and without OBBBD, has never been studied to this day. We hypothesize that the IA delivery of TMZ, with or without OBBBD, will increase its concentration in the CNS. Also, its delivery by these methods and its combination to radiotherapy will intensify its anti-neoplastic activity. In the Fischer-F98 model, the Kaplan-Meier survival curves show a decreased survival with increasing doses of TMZ (IA group). Against all odds, no differences in survival were shown between the IA with/without OBBBD versus IV/control groups. For each method of delivery, the addition of radiotherapy increased survival. Only the groups receiving TMZ intra-arterially (with/without OBBBD) demonstrated adverse effects. The combination of TMZ to radiotherapy seems to increase survival in the Fischer-F98 model. However, TMZ looks to be toxic when administered intra-arterially, most likely due to greater effects during its first passage through the cerebral circulation. Despite available data that TMZ is well tolerated clinically (oral administration), predicting its toxicity and its anti-neoplastic activity when delivered by alternative methods in this animal model is difficult.

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A role for matrix remodeling proteins in invasive and malignant meningiomas

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Aims: Meningiomas are one of the most common brain tumors in adults. Invasive and malignant meningiomas present a significant therapeutic challenge due to high recurrence rates and invasion into surrounding bone, brain, neural and soft tissues.