P01.23 Genetic analysis of malignant transformation in glioma with 1p19q LOH

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To develop novel therapeutics targeting GSCs, we screened drug A. Glioma is a CNS tumor resulting from accumulation of genetic mutations. Glioblastoma stem cell (GSC)-targeted therapy is a promising treatment for patient with glioblastoma (GBM). However, none of the drugs that target the brain-penetrating properties of essential for GSC maintenance has been put to clinical use. Here we identified fluspirilene, a chronic schizophrenia and psychotic drug, as a new drug candidate for treating GBM. Over thousands of existing drugs and investigated the therapeutic effect of fluspirilene against GBM based ondrug repositioning. MATERIALS AND METHODS: To develop novel therapeutics targeting GSCs, we screened drug library consisting of over 10,000 compounds with brain-penetrating properties. RESULTS: The drug affected proliferation and invasion in glioma cells and mice model treated with the drug. These effects were associated with inactivation of STAT3. CONCLUSIONS: Repositioning of fluspirilene selected from the drug library is a promising approach for the therapy against GBM. Grants and fellowships: Grant-in-Aid for Scientific Research (B-26293322) from the Japan Society for the Promotion of Science.

OBJECTIVE: Gliomas are the most common primary tumors of the central nervous system (CNS), but despite advances in therapy these tumor remain associated with poor prognosis. The MGMT gene is epigenetically silenced by promoter hypermethylation in gliomas, and this modification has emerged as a relevant predictor of therapeutic response and of good prognosis. Studies with pyrosequencing (PSQ) showed that this technique has a good prediction of survival in addition to high reproducibility and sensitivity than other techniques. However, cut-off values for the percentage methylation are one of the critical issues to determine methylation status using PSQ analysis. Aim of the study is to define the cut-off value correlated with good favorable prognostic outcome. METHODS: We collected a tumor samples of glioma patients who underwent the follow-up of one of the Neuro-oncology Unit of the National Cancer Institute Regina Elena will be included in this study. We collected demography, clinical and molecular data, as well as data on response to treatments and outcomes (PFS and OS). For pyrosequencing method, we used the MGMT Plus kit (Diatech Pharmagenetics, Jesi, Italy) according to the manufacturer's protocol. Modified DNA was subjected to PCR amplification with a forward primer and a biotinylated reverse primer using the MGMT PLUS Kit (Diatech pharmagenetics) and “Rotor-Gene 6000” equipment. We performed pyrosequencing methylation assay to evaluate 10 CpG sites in the following regions: chr 10:131,265,507-131,265,556 using sequencing primer of MGMT Kit Diatech Pharmagenetics, Jesi (Ancona), Italy. The pyrosequencing analysis was performed with PyroMarker CpG Software 1.0.11 (Qiagen). The software calculated the percentage methylation for each 10 CpG sites and the total mean of all 10 CpG sites. RESULTS: We enrolled 177 patients of glioma analyzed with PSQ for MGMT and IDH1. Of them 102 patients were females and 75 are males. The majority of patients are affected by Glioblastoma. Statistical analysis showed that a percentage of methylation higher than 35% resulted significantly correlated with higher PFS respect to a percentage of methylation lower than 35%. Patient with cut off <35% have a rate of PSF at 1 years of 53% while only 4.2% of patients with cut off <35% have a disease progression free at 1 year. Discussion: Our data showed that patients with a cut-off <35% had a shorter PFS but not significant different was observed in terms of overall survival. Other studies are warranted on larger population to validate these data.

BACKGROUND: Glioblastoma (GBM) accounts for approximately 50% of all glioma and among these tumors, are the most malignant. The current standard of care for patients with newly diagnosed GBM includes temozolomide and radiotherapy. Melanocortins are peptides with well-recognized anti-inflammatory and neuroprotective activity. No data are currently available on MC4R gene polymorphisms and gliomas or their relationship with radiotherapy or chemotherapy. Given the association of MC4R with anti-inflammatory activity, neuroprotection, induction of neural stem/progenitor cell proliferation in brain hypoxia, and prevention of astrocyte apoptosis, the aim of this study was to retrospectively evaluate the possible prognostic/predictive role of the MC4R SNPs on GBM therapy. METHODS: Sixty-one patients with a proven diagnosis of GBM, ECOG PS 0–2, age greater than 18 years, and treated with radiotherapy and temozolomide were enrolled. Blood samples (3 ml) were collected in EDTA tubes and stored at 80°C. Genomic DNA was extracted using QIAamp DNA Blood Mini Kit. MC4R gene SNPs (rs17782313, rs489693, rs8087522, rs17700633) were analyzed; the allelic discrimination was performed using an ABI PRISM