meningiomas (Khaddar et al., South Asian J Cancer 9:261, 2020). Besides its efficacy as a single agent, gemcitabine reportedly has a radiosensitizing effect in pancreatic cancer. However, it remains unknown whether or how gemcitabine interacts with ionizing radiation (IR) in malignant meningioma cells. METHODS: We examined radiosensitization effects of gemcitabine using malignant meningioma cell lines and xenografts (s.c. and i.c.) and explored the underlying mechanisms. RESULTS: Gemcitabine sensitized malignant meningioma cells remarkably to IR through the induction of senescence both in vitro and in vivo. Gemcitabine augmented the intracellular production of reactive oxygen species (ROS) by IR, which, together with cell growth suppression/senescence induced by this combination, was inhibited by N-acetyl-cysteine, suggesting a pivotal role for ROS in these combinatorial effects. Navitoclax, a senolytic drug, further enhanced the effects of the combination of gemcitabine and IR in vitro and in vivo by strongly inducing apoptotic cell death in senescent cells. CONCLUSION: These results suggest that gemcitabine is not only a promising radiosensitizer for malignant meningioma but also creates in combination with IR a therapeutic vulnerability of senescent meningioma cells to senolytics. (submitted for publication)

Key words: meningioma | gemcitabine | senescence

ET-7

ROLES FOR HENT1 AND DCK IN GEMCITABINE SENSITIVITY AND MALIGNANCY OF MENINGIOMA

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Background: High-grade meningiomas are aggressive tumors with high morbidity and mortality rates that frequently recur even after surgery and adjuvant radiotherapy. However, limited information is currently available on the biology of these tumors, and no alternative adjuvant treatment options exist. Although we previously demonstrated that high-grade meningioma cells were highly sensitive to gemcitabine in vitro and in vivo, the underlying molecular mechanisms remain unknown. Methods: We examined the roles of hENT1 (human equilibrative nucleoside transporter 1) and dCK (deoxycytidine kinase) in the gemcitabine sensitivity and growth of meningioma cells in vitro. Tissue samples from meningiomas (26 WHO grade I and 21 WHO grade II/III meningiomas) were immunohistochemically analyzed for hENT1 and dCK as well as for Ki-67 as a marker of proliferative activity. Results: hENT1 and dCK, which play critical roles in the intracellular transport and activation of gemcitabine, respectively, were responsible for the high gemcitabine sensitivity of high-grade meningioma cells and were strongly expressed in high-grade meningiomas. hENT1 expression was required for the proliferation and survival of high-grade meningioma cells and dCK expression. Furthermore, high hENT1 and dCK expression levels correlated with stronger tumor cell proliferative activity and shorter survival in meningioma patients. Conclusions: The present results suggest that hENT1 is a key molecular factor influencing the growth capacity and gemcitabine sensitivity of meningioma cells and also that hENT1, together with dCK, may be a viable prognostic marker for meningioma patients as well as a predictive marker of their responses to gemcitabine.

Key words: meningioma | gemcitabine | hENT1

ET-8

INTEGRATED DIAGNOSTIC APPROACH TO PREDICT PROGNOSIS FOR MALIGNANT GLIOMAS

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Previous studies indicated that MGMT promoter methylation status with IDH and TERT promotor mutation are major prognostic factors in glioma. In addition to these molecular features, we have been assessing drug sensitivity against several chemotherapeutic agents, including temozolomide (TMZ). Here, we examined if this combined information could strongly predict drug sensitivity and the prognosis in glioma patients. One hundred and twenty-five IDH wild-type gliomas (WHO grade III and grade IV) were included in this study and retrospectively analyzed. Among them, we focused on 37 patients with partial surgical resection and biopsy to assess radiological difference on MRI. The primary cultured tumor cells were exposed with several compounds for 72 hours, then ATP based cell viability assay was performed. The favorable radiological therapeutic effect was found in 6 out of 8 (75%) with MGMT promoter methylated cases, while unfavorable in 23 of 29 (79.3%) with MGMT promoter unmethylated cases (p=0.008). The drug screening assay demonstrated that 7 of 10 cases with favorable TMZ sensitivity in vitro showed response on MRI, whereas 22 of 27 (81.5%) cases with TMZ resistance in vitro indicated tumor progression (p=0.006). Of note, all 5 cases with sensitive to TMZ and methylated MGMT promoter demonstrated favorable radiological response (p=0.002). These 5 cases tended to survive longer (median survival time, 697 days) as compared to others (median survival time, 391 days, p=0.13). These data indicate that integrated approach with genomic assessment and drug screening test may predict therapeutic response to chemotherapy and contribute selecting optimal therapy in glioma patients.

Key words: Prognostic prediction | Temozolomide | MGMT

ET-9

DEVELOPMENT OF PHOTOSENSITIVE ANTIBODIES FOR NEAR-INFRARED LIGHT IMMUNOTHERAPY TARGETING EGFR AND IL13RA2 OF MALIGNANT GLIOMAS AND INVESTIGATION OF THEIR PHOTODYNAMIC CYTOTOXIC ACTIVITY IN VITRO

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Introduction: Near-Infrared Photoimmunotherapy (NIR-PIT) is a recently developed hybrid cancer therapy based on photodynamic cytotoxicity and anti-tumor immunopotentiation, utilizing a photosensitive antibody drug (PSAD). A global Phase III trial of NIR-PIT with an anti-EGFR-PSAD in patients with recurrent head and neck squamous cell carcinoma (HNSCC) is already underway, and NIR-PIT is expected to have therapeutic applications also in malignant gliomas. Methods: In this study, monoclonal antibodies to EGFR and IL13Rα2 were conjugated to the photosensitive dye IRDye700DX (IR700) to produce PSADs (EGFR-Ab/IR700 and IL13Rα2-Ab/IR700) and in vitro PDT assays using these PSADs were performed on four human glioma cell lines (U87MG, U251, U138, A172).Five groups were studied: EGFR-Ab/IR700 monotherapy: 5 μg/ml or 10 μg/ml, IL13Rα2-Ab/IR700 monotherapy: 5 μg/ml or 10 μg/ml, and EGFR-Ab/IR700: 5 μg/ml + IL13Rα2-Ab/IR700: 5 μg/ml combination therapy. The cytotoxic activity of each group was compared after irradiation with 690 nm light at 16 J/cm2. Results: Significantly higher cytotoxic activity was observed in all four glioma cell lines when EGFR-Ab/IR700 and IL13Rα2-Ab/IR700 were used in combination at 5 μg/ml each, than when each PSAD was treated with a doubled dose (10 μg/ml).Conclusion: Malignant gliomas show extensive cellular heterogeneity with diverse expression of cell surface antigens. The present results suggest that a therapeutic strategy using several different photosensitive antibodies simultaneously may lead to the release of tumor antigens from a greater number of tumor cells, resulting in a more efficient host immune response for therapeutic purposes.

Key words: Photoimmunotherapy | EGFR | IL13Rα2

TUMOR BIOLOGY/MODELS (TB)

TB-2

PATIENT-DERIVED MENINGIOMA ORGANOID MODEL DEMONSTRATES *FOXM1* DEPENDENT TUMOR PROLIFERATION

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Recent comprehensive studies have revealed several molecular alterations that are frequently found in meningiomas. However, effective treatment reagents targeting specific molecular alterations have not yet been identified because of the limited number of representative research models of meningiomas.

We established 18 organoid models comprising of two malignant meningioma cells (HKBMM and IOMM-Lee), 10 benign meningiomas, four malignant meningiomas, and two solitary fibrous tumors (SFTs). Using immunohistochemistry and molecular analyses consisting of whole exome sequencing, RNA-seq, and DNA methylation analyses, we compared the histological findings and molecular profiling of organoid models with