

brain indicating that RXFP1 signaling in GB is activated by auto-/paracrine secretion of CTRP8. In GB, RXFP1 signaling included PI3K and PKC activation and resulted in the increased production and secretion of lysosomal protease cathepsin B, a known prognostic marker of GB. In the present study, we have investigated the potential role of RXFP1 in chemoresistance to the commonly used DNA alkylating drug temozolomide (TMZ) in human GB. Upon TMZ treatment, CTRP8/RLN2 mediated activation of RXFP1 was able to mitigate DNA damage in human primary GB cells and enhanced their survival. Activation of RXFP1 resulted in STAT3 pathway activation and the RXFP1- and STAT3-dependent up-regulation of proteins and their activity deemed important for TMZ-induced DNA damage repair. Furthermore, RXFP1 activation resulted in the up-regulation of key anti-apoptotic factors in human GB cells. Our results indicate a novel role for the CTRP8-RXFP1 ligand-receptor system in STAT3-dependent cell invasion, TMZ chemoresistance, and survival and identify RXFP1 as a new protective G protein coupled receptor in GB cells.

PS2 - 217

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Treatment of Glioblastoma Brain Tumor-Initiating Cells with Microglial and Macrophage-Derived Cytokines

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The most common brain cancer, glioblastoma (GBM), also has the worst five-year survival rates of all cancers. This is due in part to cancer stem cells, known as brain tumor initiating cells (BTICs), which initiate GBM and are resistant to current therapies. Thus, it is important to study therapeutics targeting BTICs. Innate immune cells, microglia and macrophages (MMs), are also important GBM-associated cells. GBM influences MMs to promote tumor growth. However, my research group discovered that an old drug, amphotericin B, re-stimulates MMs to secrete cytokines that inhibit BTIC self-renewal (Nature Neurosci 17:46-55, 2014). Hence, I hypothesize these cytokines are potential GBM treatments. Methods: Twenty genetically diverse BTIC lines were exposed to interleukin-8 (IL8), monocyte chemoattractant protein-1 (MCP1), and tumor necrosis factor-alpha (TNF), the cytokines secreted most abundantly by amphotericin-stimulated MMs. Assays for proliferation, differentiation, apoptosis, and cell cycle arrest were performed. BTICs were then co-cultured with human GBM-derived MMs stimulated with TNF. Lastly, the relationship between TNF receptors (TNFR1/2) and presumed BTICs was determined in frozen human GBM sections by immunofluorescence. Results: TNF had the most potent inhibitory effect on BTIC proliferation. Also, TNF was able to increase BTIC differentiation, and induce apoptosis and G1 cell cycle arrest. In MM-BTIC co-culture, TNF stimulated MMs to decrease sphere formation. Interestingly, in human GBM tissue TNFR1 co-labeled with OLIG2, a major transcription factor expressed in presumed BTICs, implicating TNF as a BTIC-specific treatment. Conclusion: TNF is a promising candidate for the treatment of GBM.

PATHOLOGY

PS2 – 195

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Integrating Molecular Workings into the World Health Organization (WHO) Classification of Tumours of the Central Nervous System: A Survey from the Neuro-Oncology Community

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Tumours of the central nervous system are currently classified based on the 2007 WHO Classification of Tumours, which uses histological features to classify and grade these heterogeneous tumors. With recent advances in the development of clinically relevant molecular signatures, there is an interest to incorporate appropriate molecular markers in to the classification. The views of the neuro-oncology community on such changes would be informative for advising this process. METHODS A survey with 8 questions regarding molecular markers in tumor classification was sent to an email list of Society of Neuro-Oncology members and attendees of prior meetings (n=5065). There were 403 respondents. Analysis was performed using whole group response and based on self-reported sub-specialty. RESULTS Survey results among all respondents show support for incorporating our molecular knowledge of brain tumors into the WHO classification (>80%). As one example, 96% of respondents responded that the integration of 1p/19q co-deletion into the molecular classification of oligodendroglioma was “very” or “critically” important for the management of grade III gliomas. While 30% of all respondents believe that IDH mutation status should affect overall management of GBM. Interestingly, there was some variability among sub-specialties for certain aspects, and as one example neuropathologists were slightly more inclined to disagree that molecular markers should be included in the WHO classification (25% for neuropathologists versus 13% overall). CONCLUSION Based on a survey provided to the neuro-oncology community, we report strong support for the integration of molecular markers into the WHO classification of brain tumors, as well as for using an integrated “layered” diagnostic format.

PS2 - 205

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Application of Computer-Assisted Diagnostics for Immunohistochemistry Analysis of Gliomas

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In the current practice of pathology, the identification of cell markers and their respective distribution represents an indispensable dialogue for diagnostic, predictive, therapeutic, and research purposes. Early immunohistochemical protocols were limited to direct, fluorescent labeled antibodies, yielding quick results but lacking sensitivity. More recently, the use of indirect techniques –utilization of enzyme labels – and various detection systems have continued to advance the complexity of IHC,

increasing both its specificity and sensitivity of detecting one or multiple antigen(s) (Ag) simultaneously. As such, IHC has become an affordable, powerful, and readily available means for the identification of candidate biomarkers (mostly lineage markers) in formalin-fixed, paraffin-embedded (FFPE) tissue samples. Pathologists are now asked to “quantify” expression levels of differential prognostic markers –at microscopic level – using this arguably “non-quantitative” technique. Conventionally, histological grading relies mainly on manual counting of positively immunostained cells, a labour intensive protocol that may be associated with subjectivity, intra- and inter- observer variation and reproducibility issues. The subjectivity and lack of reproducibility has prompted the use of computer-assisted or fully automated image analysis technologies. Digital image acquisition systems are becoming commonplace and as such, the demand for complex assessments of digital images of histological slides must be matched with quantitative platforms. In this study, we aim to introduce a computer-assisted image-computing platform that is both accurate and efficient in quantification of isolated and heterogeneous candidate biomarkers in glioblastoma.

IMAGING

PS2 – 196

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Investigating the Spatial Agreement Between Pre-Operative Functional MRI and Intra-Operative Direct Cortical Stimulation

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Pre-operative functional magnetic resonance imaging (fMRI) has emerged as valuable clinical tool to help surgically manage patients diagnosed with brain tumours. Surgical decision-making may be significantly improved through the provision of fMRI, however its clinical usage is contingent on the level of agreement with direct cortical stimulation (DCS). While previous studies have been undertaken to investigate the spatial agreement between fMRI and DCS, the influence that various factors may have on fMRI sensitivity and specificity is not fully clear. Thus, in a group of eight brain tumour patients who underwent pre-operative fMRI followed intra-operative DCS during an awake craniotomy procedure, we measured the agreement between the two brain mapping techniques looking at the influence of behavioural task, statistical threshold, and task standardization. Results: There were significant differences between motor and language mapping, where agreement was better for the former. Sensitivity and specificity shared an inverse relationship with increasing fMRI threshold, and were significantly reduced in the case where tasks were not standardized. Lastly, false positive occurrences were identified as the dominate source of error in comparison to false negative occurrences. Conclusion: Thus, the results from this work suggest that fMRI can predict intraoperative findings with good accuracy, however, sources of variability may significantly reduce the quality of fMRI data at the single-subject level. Neurosurgeons should carefully evaluate fMRI data with these considerations prior to its inclusion in the surgical-decision making process.

CLINICAL POSTER VIEWING SESSION III 11 JUNE 2016 ~ 1000 - 1045

GLIOMA CLINICAL

PC3 – 151

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Toca 5: A Phase 2/3 Randomized, Open-Label Study of Toca 511, a Retroviral Replicating Vector, Combined with Toca FC versus Standard of Care in Patients Undergoing Planned Resection for Recurrent Glioblastoma (GBM) or Anaplastic Astrocytoma (AA) (NCT02414165)

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Recurrent GBM and AA have a dismal prognosis and a high unmet need for effective therapies. Toca 511 (vocimagene amiretrorepvec) is an investigational retroviral replicating vector that encodes the transgene cytosine deaminase (CD). Toca 511 selectively infects, persists and spreads in tumor. Subsequent oral administration of 5-fluorocytosine (Toca FC) produces 5-fluorouracil (5-FU) by CD within infected cells. 5-FU kills cancer cells and myeloid derived suppressor cells, inducing robust antitumor immune responses in animal models. Clinical data from phase 1 trials are consistent with this mechanism of action, and show extended survival compared to historical controls. Toca 5 is a multicenter, randomized, open-label Phase 2/3 trial of Toca 511 and Toca FC versus standard of care administered to patients undergoing resection for first or second recurrence of GBM or AA. Phase 2 will enroll 170 patients. Primary endpoint is overall survival (OS). Key secondary endpoints are safety, objective response rate, clinical benefit rate, progression-free survival, and landmark OS. Key inclusion criteria are age 18-75 years, histologically proven GBM or AA, measurable disease preoperatively of less than 5cm, candidate for equal or greater 80% resection of enhancing tumor based on pre-operative evaluation, and KPS equal or greater to 70. Assays for immune monitoring will be performed and molecular profiling of resected tumor samples will be correlated efficacy.

PC3 – 152

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Impact of Extent of Resection Upon Outcome in Newly Diagnosed Glioblastoma: A Study in the Molecular Era

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For decades, debate has persisted regarding the role of surgical resection in newly diagnosed glioblastoma. There is increasing evidence that extent of resection (EoR) is an independent prognostic factor. Previous work has proposed the inclusion of EoR in a risk stratification algorithm but does not incorporate