

Understanding the molecular mechanism of invasion could help in designing novel therapeutic approaches in order to prevent the need for repeat surgery, decrease morbidity and improve patient survival. The aim of this study was to identify the key factors and underlying mechanisms which govern invasive properties of meningiomas. Methods: Towards this end, we performed gene expression profiling of invasive and non-invasive meningioma tumors. Matrix metalloproteinases (MMPs) 16 and 19 were among the genes associated with cell movement and invasion. Results & Discussion: We establish that the expression level of MMP16 was significantly elevated in both bone-invasive and brain invasive meningiomas. Gain- and loss-of-function experiments indicated a role for MMP16 in meningioma cell movement, invasion and tumor cell growth. Furthermore, MMP16 was shown to positively regulate MMP2, suggesting this mechanism may modulate meningioma invasion in invasive meningiomas. Conclusions: Overall, the results support a role for MMP16 in promoting invasive properties of the meningioma tumors. Further studies to explore the potential value for clinical use of matrix metalloproteinases inhibitors, perhaps specifically targeting MMP16 are warranted.

P1 – Session3 1615-1625

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Neural derivatives from human embryonic stem cells: modelling early cellular and molecular events contributing to Depediatric brain tumorigenesis

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Malignant brain tumors are among the most prevalent forms of childhood cancers. The extensive genetic, molecular and clinical heterogeneity within subtypes has made it difficult to assess the functional relevance of genes to malignant progression. For example, medulloblastoma is classified into four molecular subgroups; Wnt, Sonic hedgehog, Group 3 and Group 4, based on genetic alterations and molecular signatures. Among these molecular signatures, a homeodomain transcription factor, Orthodenticle homeobox2 (Otx2), is frequently amplified and overexpressed in medulloblastoma; however, the functional relevance of Otx2 may indeed be subtype-specific. We recently demonstrated that neural precursors derived from neoplastic human embryonic stem cells (hESCs), but not their normal counterparts, model pediatric brain tumors in vivo and exhibit

high Otx2 expression. Here, we used this hESC-based model system to further delineate the role of Otx2 in normal human neurodevelopment and medulloblastoma progression using gain and loss of function studies. Parallel experiments with well-established brain tumor cell lines support the subtype-dependent tumor suppressive or oncogenic role of Otx2 in medulloblastoma. Otx2 overexpression resulted in an overall repressive effect on cellular functions such as cell proliferation, migration and self-renewal and this was accompanied by global downregulation of hESC pluripotency genes. While knockdown of Otx2 also suppressed cellular functions, this appears to be less dependent on hESC gene regulation. Our study reveals a novel link between Otx2 and hESC genes that may contribute to both human neurodevelopment and medulloblastoma progression and validates our hESC-derived system as an alternative model for studying the mechanisms underlying pediatric neural tumorigenesis.

P2 – Session3 1625-1635

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Targeting the base excision repair pathway to overcome therapeutic resistance to alkylating agents in pediatric glioblastoma

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Alkylating agents are a common frontline therapy for the treatment of several cancers including pediatric glioblastoma (pGBM), a devastating lethal tumor in children. Unfortunately, many tumors are resistant to this therapy and traditional mechanisms of resistance including MGMT promoter methylation fail to fully explain treatment resistance in pGBM. We sought to identify ways of sensitizing tumor cells to alkylating agents while leaving normal glia and neural stem cells unharmed; increasing therapeutic response while minimizing toxicity. An siRNA screen targeting over 240 DNA damage response genes identified novel sensitizers to alkylating agents, namely temozolomide. In particular the base excision repair (BER) pathway, including DNA-3-methyladenine glycosylase (MPG), as well as ataxia telangiectasia mutated (ATM) were identified in our screen. ATM, MPG and BER were required for allowing tumour cells to repair damaged DNA and survive exposure to temozolomide. Patients with high expression of MPG had poorer overall survival compared to MPG low expressing patients and that MPG was one the most commonly amplified genes of the BER pathway in pGBM. Combined inhibition or loss of MPG and ATM resulted in increased alkylating agent-induced cytotoxicity in vitro and prolonged survival in vivo using several orthotopic mouse models of pGBM. Further, we identified, several small molecule inhibitors of BER that effectively sensitized pGBM cells to clinically relevant doses of TMZ and prolonged survival in vivo. Inhibition of ATM and BER cooperate to sensitize tumour cells to alkylating agents, impairing tumour

growth in vitro and in vivo with no toxicity to normal cells providing an ideal therapeutic window.

P3 – Session3 – 1635-1645

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The impact of initial radiation in infants and the re-irradiation of recurrent disease on the survival of ependymoma patients at The Hospital for Sick Children, Toronto

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Background: Two significant changes in ependymoma management have recently been made at Sickkids Hospital, Toronto; the up-front irradiation of infants and re-irradiation of recurrent disease. The impact of these on survival was retrospectively evaluated. **Methods:** A retrospective case note analysis of ependymoma patients between 1990 and 2014 was undertaken. Survival was determined using the Kaplan Meier method. **Results:** 76 ependymoma patients were identified (median age 4.58 years (0.42-17.6)), including 31 infants < 3 years (median age 1.51 years (0.42-2.97)). The median progression-free survival (PFS) and overall survival (OS) was 41 months (95% CI 20.4-61.7) and 116 months (95% CI 63.5-169.4) respectively. 5 year PFS and OS were 43.3% and 59.3% respectively. 21 infants received up-front radiation and 10 chemotherapy only. 5 year PFS and OS were significantly higher in irradiated compared to non-irradiated infants (PFS: 52.9% versus 0% (p=0.00002), OS: 74.6% versus 30.0% (p=0.004)). 38 patients recurred of which 26 were previously irradiated. 19 patients received re-irradiation on recurrence, 7 did not. 5 year OS was significantly higher in re-irradiated patients (71.8%) compared to non re-irradiated patients (0%) (p=0.00007). Both management strategies were consistently implemented from 2004. Patients treated pre (n=34) and post (n=42) 2004 showed significant improvement in 5 year PFS from 33.4% to 53.3% (p=0.037) and OS from 51.2% to 79.2% (p=0.02). **Conclusions:** Both radiation of infants as the initial management of ependymoma and re-irradiation of recurrent ependymoma significantly improves survival. Implementing these treatment strategies has resulted in significant improvement in progression free and overall survival for ependymoma patients.

P4 – Session3 1645-1655

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Outcomes of children with central nervous system (CNS) germinoma treated with carboplatin-based chemotherapy followed by reduced radiation

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Background: Central nervous system (CNS) germinomas have an excellent prognosis with radiation therapy alone. However, in children, volume and dose of CNS radiation impact long-term morbidity. Cooperative groups have modified therapy by giving chemotherapy followed by reduced CNS radiation to minimize morbidity. **Methods:** This retrospective cohort study analyzed the outcome of intracranial germinoma patients treated at SickKids in Toronto, Canada, from January 2000- December 2013. **Results:** 25 children (14 male, 11 female; median age 12.92 years; range 6-17 years) were identified. Median follow up was 61 months (range 1-144 months). Median duration of symptoms pre-diagnosis was 5 months (range 1-36 months). Tumor location was suprasellar (n=9), bifocal (8), pineal (6), and basal ganglia (2). Three children had ventricular and one child had craniospinal dissemination. 2/25 had only elevated serum human chorionic gonadotropin (HCG, mean 13.5 IU/L), 4/25 only elevated lumbar CSF HCG (mean 21.3 IU/L), and 2/25 had both elevated serum and lumbar CSF HCG (mean 23 and 41.5 IU/L respectively). 24/25 children completed treatment and received carboplatin-based chemotherapy followed by either ventricular irradiation (23.4-24 Gy) ± boost (16 Gy) (n=15), whole brain (23.4 Gy) (n=3), focal (40 Gy) (n=4) or craniospinal irradiation (23.4 Gy) (n=2). Five-year progression free and overall survival were 96% and 100% respectively. Education status was available for 11/16 survivors now >18 years of age. Of those, 1 completed grade school, 3 completed high school and 7 are attending college/university. **Conclusions:** Our data suggests excellent survival with combined treatment modality and great potential for academic success.

CLINICAL ORAL PRESENTATIONS

14 June 2014

C1 – Session5 1030-1045

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Behavioral syndromes in patients with brain tumors using the Frontal System Behavior Scale (FrSBe)

(Young Investigator Award Winner - Clinical Research)

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