such as melanoma, but not against GBM in part because GBM-associated MMs are not well understood. We hypothesized the content and inflammatory phenotype of MMs in GBM is variable between patients. We suspect MMs in IDH-wildtype and –mutant GBMs display divergent inflammatory phenotypes that helps explain the latter's better prognosis. Understanding GBM-associated MM heterogeneity will allow for better immunotherapy development and selection. Methods: MMs were isolated from untreated human IDH-wildtype and -mutant GBMs using flow cytometry and cultured for collection of conditioned media and analysis of secretory products. Automated segmentation with a high-content analysis system was used to quantitate MM content and inflammatory phenotype in frozen sections. New bioinformatics techniques allowed the comparison of MM profiles in publicly available single-cell RNA-sequencing databases with IDH-wildtype and -mutant GBMs. Results: Surprisingly marked variation in MM content exists between GBMs ranging from ~0-70%. A mixture of pro- and anti-inflammatory MMs are found in each GBM. Interestingly, IDH-mutant GBM-associated MMs were more activated than MMs in IDH-wildtype GBMs. Conclusions: Taken together, the highly variable MM content and phenotype of GBMs suggests the success of immunotherapies hinges on taking a precision medicine approach. MM-rich GBMs would benefit more from therapies that target them. MM activation in IDH-mutant GBMs may contribute to better patient prognoses.

18

doi:10.1017/cjn.2018.304

Peroxiredoxin1 is a therapeutic target in group-3 medulloblastoma

Sajesh, BV., Ngoc, OH., Omar, R., Fediuk, H., Li, L., Alrushaid, S., Wang, W., Pu, J., Sun HD., Siahaan, T., Werbowetski-Ogilvie, T., Wölfl, M., Remke M., Ramaswamy, V., Taylor, M., Eberhart, C., Symons, M., Ruggieri, R., Miller, DW & Vanan, MI.
bsajesh@cancercare.mb.ca

Group-3 medulloblastoma (MBL) is highly resistant to radiation (IR) and chemotherapy and has the worst prognosis. Hence, there is an urgent need to elucidate targets that sensitize these tumors to chemotherapy and IR. Employing standard assays for viability and sensitization to IR, we identified PRDX1 as a therapeutic target in Group-3 MBL. Specifically, targeting PRDX1 by RNAi or inhibition by Adenanthin led to specific killing and sensitization to IR of Group-3 MBL cells. We rescued sensitization of Daoy and UW228 cells by hypermorphic expression of PRDX1. PRDX1 knockdown caused oxidative DNA damage and induced apoptosis. We correlated PRDX1 expression to patient outcomes in a validated MBL tumor-microarray. Whole genome sequencing identified pathways/genes that were dysregulated with PRDX1 inhibition or silencing. Our in vivo studies in mice employing flank/orthotopic tumors from patient derived xenografts/Group-3 MBL cells confirmed in vitro observations. Animals with tumors in which PRDX1 was targeted by RNAi or Adenanthin (using mini osmotic pumps) showed decreased tumor burden and increased survival when compared to controls. Since, Adenanthin does not cross the blood brain barrier (BBB) we used HAV6 peptide to transiently disrupt the BBB and deliver Adenanthin to the tumor. Immunohistochemistry confirmed that targeting PRDX1 resulted in increased oxidative DNA damage, apoptosis and decreased proliferation. In summary, we have validated PRDX1 as a therapeutic target in group-3 MBL, identified Adenanthin as a potent chemical inhibitor of PRDX1 and confirmed the role of HAV peptide (in the transient modulation of BBB permeability) in an orthotopic model of group-3 MBL.

ORAL PRESENTATIONS
12 MAY 2018

1105-1150 SELECTED CNO2018 ABSTRACTS

09

doi:10.1017/cjn.2018.305

Could DLX2 regulation of neural progenitor cell fate contribute to differentiation of diffuse intrinsic pontine glioma (DIPG)?

Nevin M, Song X, Japoni S, Zagozewski J, Jiang Q, Becher O, Godbout R, Underhill DA, Eisenstat DD. eisensta@ualberta.ca

Introduction: Diffuse intrinsic pontine glioma (DIPG) is refractory to therapy. The identification of histone H3.1/H3.3 K27M mutations in most DIPG has provided new insights. The DLX homeobox genes are expressed in the developing forebrain. The Dlx1/Dlx2 double knockout (DKO) mouse loses tangential GABAergic interneuron migration to the neocortex. We have identified genes that encode glutamic acid decarboxylase (GAD) enzymes as direct targets of DLX1/DLX2. In DIPG patients with H3.3 K27M mutations there is decreased Dlx2 and increased expression of the myelin transcription factor, Myt1. Methods and Results: We used bioinformatics approaches and chromatin immunoprecipitation (ChIP) assays to identify Olig2, Nkx2.2 and Myt1 promoter sequences as candidate DLX2 targets in vivo. DNA binding specificity was confirmed. The functional consequences of Dlx2 co-expression with reporter constructs of ChIP-isolated promoter fragments of Olig2 and Nkx2.2 demonstrated repression of gene targets in vitro. qPCR showed increased Olig2 and Nkx2.2 expression in the DKO forebrain. Stable transfection of a murine DIPG cell line with Dlx2 resulted in increased Gad1 and Gad2 and decreased Olig2 and Nkx2.2 expression. Of significance, we demonstrated decreased expression of H3.3 K27M and restoration of H3.3 K27 tri-methylation (me3). Conclusions: DLX transcription factors promote GABAergic interneuron and concomitant inhibition of oligodendroglial differentiation in neural progenitors by repression of a suite of genes including Olig2 and Nkx2.2. Restoration of H3 K27me3 expression in DIPG provides a promising lead towards exploration of differentiation as a therapeutic strategy for DIPG.

55

doi:10.1017/cjn.2018.306

Malignant primary brain and other central nervous system tumours diagnosed in the Canadian population from 2009 to 2013

Walker, EV, Davis, F & The CBTR Surveillance and Reporting Working Group. emily.walker@ualberta.ca

The Canadian Brain Tumour Registry (CBTR) project was established in 2016 with the aim of enhancing infrastructure for surveillance and clinical research to improve health outcomes for brain tumour patients in Canada. We present a national surveillance report on malignant primary brain and central nervous system (CNS) tumours diagnosed in the Canadian population from 2009-2013. Patients were identified through the Canadian Cancer Registry (CCR); an administrative dataset that includes cancer incidence data from all provinces/territories in Canada. Cancer diagnoses are coded using the ICD-O3 system. Tumour types were classified by site and histology using The Central Brain Tumour Registry of the United States definitions. Incidence rates (IR) and 95% confidence intervals (CI) were calculated per 100,000 person-years and standardized to the 2011 census population age-distribution. Overall, 12,115 malignant brain and CNS tumours were diagnosed in the Canadian population from 2009-2013 (IR:8.43;95%CI:8.28,8.58). Of these, 6,845 were diagnosed in males (IR:9.72;95%CI:9.49,9.95) and 5,270 in females (IR:7.20;95%CI:7.00,7.39). The most common histology overall was glioblastoma (IR:4.06;95%CI:3.95,4.16). Among those aged 0-19 years, 1,130 malignant brain and CNS tumours were diagnosed from 2009-2013 (IR:3.36;95%CI:3.16,3.56). Of these, 625 were diagnosed in males (IR:3.32;95%CI:3.34,3.92) and 505 in females (IR:3.08;95%CI:2.81,3.36). The most common histology among the paediatric population was pilocytic astrocytoma (IR:0.73;95%CI:0.64,0.83). The presentation will include: IRs for other histologies, the geographic distribution of cases and a comparison between Canada and the United States.

56

doi:10.1017/cjn.2018.307

Unique Immune Microenvironment in NF2-Fusion Positive Radiation Induced Meningiomas

Suganth Suppiah, Jeff Liu, Yasin Mamatjan, Gelareh Zadeh.
suganth.suppiah@mail.utoronto.ca

Introduction: Radiation-induced meningiomas (RIMs) are increasing in prevalence as cancer patients live longer. Our laboratory has demonstrated that RIMs have a unique genomic landscape compared to sporadic meningiomas. Notably, a subset of RIMs harbor genomic rearrangement resulting in NF2 gene fusion with a nonrecurrent reciprocal gene. We aimed to compare the gene expression of NF2-Fusion and NF2-Wild Type (NF2-WT) RIMs. Methods: RNA sequencing using Illumina HiSeq was performed on 7 NF2-Fusion and 12 NF2-WT RIMs. Short read sequences obtained from sequencing were mapped to reference human genome(hg19). We performed differential expression analysis using edgeR statistical packages. Pathway analysis was performed using Gene Set Enrichment Analysis (GSEA). Immunohistochemistry was performed to validate findings. Results: Principal component analysis revealed that 5/7 of NF2-Fusion RIMs had similar gene expression profiles. One outlier had no chromosome 1p loss like the other NF2-Fusion RIMs. Pathway analysis demonstrated there was an upregulation of immune pathways in NF2-Fusion RIMs. Immunohistochemistry of PD-L1 revealed that 0/7 and 7/7 of NF2-Fusion tumors had positive expression in tumoral and inflammatory cells, respectively. In comparison, 6/12 of RIMs had tumoral and inflammatory cell expression of PD-L1. In addition, there was a higher CD3 lymphocyte infiltration in NF2-WT (42.2 vs. 12.4 number of cells per HPF). Discussion: Preliminary data in our lab demonstrates that NF2-Fusion tumors have a distinct immune microenvironment compared to NF2-WT tumors. Although pathway analysis indicates that NF2-Fusion RIMs have overexpression of immune pathways, immunohistochemistry reveals that inflammatory cells have positive PD-L1 expression, suggestive of immune burnout.