Abstract A1

Investigations of the functional interactions between CIC and ATXN1L in Oligodendroglioma

D. Wong, V. Leblanc, S. Chittaranjan, M. Marra, S. Yip

BC Cancer Agency, UBC, Vancouver, BC, Canada

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Oligodendroglioma (ODG) is a subtype of low grade glioma marked by unique clinical and genomic characteristics including slow predictable progression, IDH mutation, and 1p19q-codeletion. ODGs are more sensitive to treatment leading to a favorable prognosis. Recently, mutations in CIC, a gene found on chromosome 19q, have been found in up to 70% of IDH mutated, 1p19q-codeleted ODGs. The high frequency of CIC mutations in a hemizygous state indicates that loss or altered function of the CIC protein may be crucially associated with the unique biology of ODG. Previous studies of CIC have shown this protein to be a transcriptional repressor of ETS transcription factors and a negative regulator of the MAPK pathway. CIC and ataxin-1-like (ATXN1L) are also closely involved in the pathology of spinocerebellar ataxia (SCA). However, their relationship and role in brain tumour biology has yet to be elucidated. In this study, we explore the molecular, proteomic, and functional relationship between CIC and ATXN1L which may lead to unique insights on the clinical behavior of ODG as well as identify potential molecular therapeutic targets in this enigmatic brain tumour.

Abstract A2

Adult IDH-wildtype high-grade gliomas with ATRX loss : A case series

Ana Nikolic[1], John J. Kelly[2], Leslie E. Hamilton[1]

[1]Division of Neuropathology, Foothills Medical Centre, University of Calgary; [2]Department of Neurosurgery, University of Calgary

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Recent genomic advances have led to routine use of ATRX and IDH immunohistochemistry for glioma classification. Three adult patients (age range: 48-52 years) presented with focal neurological symptoms and intra-axial frontal mass lesions. Imaging features were atypical, and unusual features in two cases resulted in repeat imaging and diagnostic delay. On biopsy, all three were high-grade astrocytomas, but with variable histology, including pure GBM-PNET, and two anaplastic astrocytomas, one with gemistocytic features. All cases had diffuse ATRX loss by immunohistochemistry, strong diffuse nuclear TP53 positivity and MGMT promoter methylation. Immunohistochemistry and mutation analysis by SNaPshot single-nucleotide extension PCR for IDH1/2 mutations was negative. A SNaPshot assay revealed the G34R mutation in H3F3A in two cases. Mutations in H3F3A G34R were initially described in pediatric hemispheric high-grade gliomas, but this case series highlights that they may also be seen in older adults. While the prognostic significance of G34R mutations in adult glioma is unknown, testing should be strongly considered in any high-grade glioma with ATRX loss and wild-type IDH.

Abstract A3

Epigenetic landscape in IDH1 mutant glioma

Luolan Li[1], Sitanshu Gakkhar[2], Misha Bilenky[2], Annaick Carles[1], Alireza Heravi-Moussavi[2], Stephanie Cho[2], Baljit Kamoh[2], Angela Tam[2], Richard Moore[2], Andy Mungall[2], Steven Jones[2], Marco Marra[2], Stephen Yip[3], Martin Hirst[1,2]

[1]Department of Microbiology and Immunology, Michael Smith Laboratories, University of British Columbia, Vancouver, BC, V6T 1Z4, Canada; [2]BC Cancer Agency Canada's Michael Smith Genome Science Center, Vancouver, BC, V5Z 4S6, Canada; [3]Department of Pathology and Laboratory Medicine, Vancouver General Hospital, Vancouver, BC, V5Z 1M9, Canada

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Somatic mutations in isocitrate dehydrogenases 1 (IDH1) have been identified as putative drivers in gliomas, and have profound impact on the epigenome by inhibiting α-ketoglutarate-dependent dioxygenases, including Tet and histone demethylases. To understand the role of IDH mutations in tumorigenesis, we profiled the epigenomes of IDH mutant gliomas and neural progenitor cells (NPCs). Compared to NPCs, IDH mutant gliomas showed a global increase in DNA methylation enriched in CpG islands. Surprisingly, for promoter hypermethylated regions associated with differentially expressed genes, only 46% were down-regulated, enriched in Frizzled proteins in Wnt pathway. Among the promoter hypermethylated and upregulated genes, 22% were also associated with loss of H3K27me3, and 21% with gain of H3K27ac. These genes were enriched in neurogenesis, including key transcription factors in neuronal differentiation such as LHX5. In addition, we found hypomethylation highly enriched in enhancers. These enhancers were enriched for binding sites of neuronal differentiation regulators, such as ASCL1 and OLIG2, both were up-regulated in IDH mutant gliomas and activated genes that promotes cell proliferation.

Abstract A4

Tumefactive MS, sentinal lesion, and PCNSL : a diagnostic conundrum

Edward Johnson

Department of Laboratory Medicine and Pathology, University of Alberta

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Distinction between tumefactive MS and sentinel lesion of PCNSL poses a diagnostic conundrum, as exemplified in this report of a 46-year-old man who presented with partial complex seizures, prompting a right temporal resection. Multiple cerebral lesions were detected by MRI 41/2 years later, necessitating a biopsy, after which he developed a brainstem syndrome. Over the 3 years thereafter, three severe relapses occurred referable to transient lesions in the cerebrum (one lesion biopsied), brainstem, and cerebellum. Presumptive diagnosis was tumefactive MS with control by combination of immunosuppressive/modulatory therapies. Emergence of an enlarging left cerebellar mass precipitated death.

Different facets of an inflammatory demyelinative process were demonstrated in the resection specimen and biopsies.

Autopsy, however, disclosed a diffuse large B-cell lymphoma in the cerebellum with widespread dissemination throughout the brain. In the background were multifocal gliotic regions of myelin/axonal loss with intermixed infiltrates of T-cells and microglia/macrophages. The biopsy sites and resection cavity showed similar findings. Overlapping features between these chronic lesions and that in the surgical specimens suggest a shared pathogenesis, supporting a concept that the sentinel lesion represents a reaction to an emerging PCNSL, either immune mediated or resorptive due to spontaneous or induced regression. Moreover, as demonstrated, PCNSL should remain a persistent consideration in the differential diagnosis, even though clinical, imaging, and pathology indices may fail in resolution between tumefactive MS, sentinel lesion, or overt PCNSL.

Abstract A5

Intraventricular ganglioglioma with hemorrhage

W. Warnica, J.P. Provias

McMaster University, Hamilton, Ontario

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Gangliogliomas represent a rare form of neuroepithelial tumours, which even more rarely present with hemorrhage or localize intraventricularly. To date, only two cases of ganglioglioma with both of these features have been reported. Our patient is a 23-year-old woman who presented with signs and symptoms of increased ICP, with a post-subtotal resection diagnosis of WHO Grade I ganglioglioma localizing bilaterally to the lateral ventricles. One year following the operation, the tumour showed radiologic evidence of interval hemorrhage, which was verified histopathologically following a second subtotal resection. Greater than 95% of the lesion represented a large hematoma with organization and well-defined fibrous pseudo-capsule, with very scanty fragments of adjacent/peripheral low-grade glial tumour. This case represents a very rare presentation of intraventricular ganglioglioma with hemorrhage.

Abstract A6

Histone H3 mutations in astrocytomas in young adult patients

DG Munoz, S Ryall, S Das, C Hawkins

St. Michael's Hospital and Hospital for Sick Children, Toronto, Ontario, Canada

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Histones are nuclear proteins involved in control of both DNA replication/repair and transcription, which are regulated by methylation and acetylation at specific residues. Recurrent point mutations have been described in histone H3 in pediatric gliomas. Using Droplet Digital (ddPCR) Assay we investigated the presence of the K27M mutation (in the genes for either H3.3 or H3.1) and G34V/R in all 39 patients under the age of 40 (over 18) operated at St. Michael's hospital for astrocytoma from 2004 to 2015 in whom enough material was available. 6 patients (average age 21 ± 5.2) harboured H3K27M mutations; tumor histology ranged from pilocytic to glioblastoma, all were located in the midline, and none was associated with mutations in IDH1 or BRAF. 10 patients (average age 30 ± 6.8) harboured H3G34R mutations; tumor histology ranged from diffuse astrocytoma to glioblastoma, all were located in the hemispheres, and were frequently associated with mutations in IDH1 (R132H, 60%) and sometimes BRAF (V600E, 10%). We also found 17 patients harboured the IDH1 R123H mutation, which co-occurred with H3G34R in 6, and 4 patients harboured the BRAF V600E, in one case along with H3G34R. Only 26% of patients did not carry at least one of the mutations investigated; Histone mutations are present in 35% of midline tumours and 40% of hemispheric astrocytomas in this age group.

Abstract A7

Impaired TDP-43 Repression of Nonconserved Cryptic Exons in Alzheimer's Disease

L Chen, WR Bell, M Sun, KD LaClair, PC Wong

Johns Hopkins School of Medicine, Baltimore, MD, USA

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Initially implicated in the pathogenesis of amyotrophic lateral sclerosis/frontotemporal dementia (ALS-FTD), TDP-43 proteinopathy has been documented in 30-70% of subjects with Alzheimer's disease (AD) neuropathology. Moreover, TDP-43 pathology has been shown to be significantly associated with cognitive impairment and brain atrophy in AD. Previously, we showed that TDP-43 serves as a splicing repressor of non-conserved cryptic exons and that such function is compromised in brains of ALS and FTD patients. It is not known whether TDP-43 cytoplasmic aggregates are a prerequisite for the incorporation of cryptic exons or how extensively such splicing defects occur in AD. Here, we report that cryptic exon incorporation occurs in all AD cases exhibiting TDP-43 pathology. Furthermore, in AD cases exhibiting both TDP-43 cytoplasmic inclusions and nuclear clearance in amygdala, but only nuclear clearance in the hippocampus, cryptic exon incorporation could still be detected in the hippocampus. These data support the notion that the depletion of nuclear TDP-43 precedes its cytoplasmic aggregation and is widespread in AD, offering important mechanistic and therapeutic implications for this devastating illness of the elderly.

Abstract A8

Patient K.C.: neuropathology of a unique case of memory impairment

A.F. Gao[1], R.S. Rosenbaum[2], F.Q. Gao[3], M. Moscovitch[2], E. Tulving[2], S.E. Black[3], J.L. Keith[1]

[1]Dept. of Anatomic Pathology, Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [2]Rotman Research Institute, Baycrest Centre for Geriatric Care, Toronto, ON, Canada; [3]L.C. Campbell Cognitive Neurology Research Group, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

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Patient K.C. has been investigated by researchers for over 20 years after intracranial trauma from a motorcycle accident resulted in a unique profile of amnesia. K.C. suffered from severe anterograde amnesia, in both verbal and non-verbal domains. This was accompanied by a selective retrograde amnesia for