OP-11-57

Monocarboxylate 8 transporter and deiodinase 2 deficiency impairs neurogliogesis in the adult mouse subventricular zone leading to cellular and functional alterations

Víctor Valcárcel-Hernández[1], Pieter Vancamp[2], Sylvie Remaud[3] & Ana Guadaño-Ferraz[1]
[1]Instituto de Investigaciones Biomédicas Alberto Sols Csic-Uam, Department of Endocrine and Nervous System Pathophysiology, Madrid, Spain; [2]Muséum National D'histoire Naturelle, Cnrs, Umr 7221, Paris, France; [3]Muséum National D'histoire Naturelle; Cnrs; Umr 7221, Paris, France

Thyroid hormones (THs) play a crucial role orchestrating neurodevelopment, but also regulate adult brain function. Recently, the potent effects that THs exert in adult neurogenic niches have started to be uncovered in rodents. These include an important role in the modulation of progenitor generation, especially controlling whether a neural stem cell (NSC) determines to become a neuronal or an oligodendroglial progenitor in the adult subventricular zone (SVZ), the largest NSC niche in the mammalian brain. A complex network of regulators tightly modulates TH availability and action, including transmembrane transporters, deiodinases and receptors. Among the TH-transporters, there is only one that is TH-specific, the monocarboxylate transporter 8 (MCT8). Deficiency of MCT8 leads to an ultra-rare but devastating disease, the Allan-Herndon-Dudley Syndrome (AHDS). Patients exhibit a plethora of endocrine and severe neurological disturbances and so far, no effective treatment for their neurological symptoms exists. Its complexity, along with its low prevalence and severe symptomatology, makes animal models and biomarkers of the disease a crucial step in the research for potential strategies to alleviate the patients' severe conditions. Using a well-validated animal model of AHDS, the *Mct8/Dio2* KO mice, we aimed to characterize how a reduced T3 availability structurally and functionally affected the neurogenic and gliogenic capacity of the adult SVZ-NSCs. To this end, we analysed the expression of cell markers by immunohistochemistry to study the balance between neurons and glia in the SVZ, both *in-vivo* and using *ex-vivo* neurosphere cultures. These studies revealed severe alterations in the neuroglial balance, with an increase of the neuron/glia ratio in the SVZ in adult *Mct8/Dio2* KO mice. We also observed that MCT8/DIO2 deficiency reduced NSC proliferation two-fold and hampered migrating of proliferating neuronal progenitors. Moreover, we tested the effects of administering exogenous THs and TH-analogues on neurospheres prepared from dissected SVZs. Neither the neuron/glia balance, nor proliferative activity responded to TH treatment in MCT8/DIO2 deficient neurospheres. Also, behaviour consequences of the observed NSCs alterations were studied using the olfactory memory and odour discrimination tests, as potential non-invasive biomarkers of the disease. These tests revealed that *Mct8/Dio2* KO mice did not recognize new odours and failed to memorize them. Altogether, these results indicate that MCT8/DIO2 deficiency severely hampers TH-dependent regulation of adult SVZ-neurogliogenesis and suggest potential biomarkers for future preclinical studies.

DOI: 10.1530/endoabs.84.OP-11-57

OP-11-58

Integrated genomic, phenomic, functional and structural mapping of variants in thyroid hormone transporter MCT8

Stefan Groeneweg[1], Ferdy Van Geest[2], mariano martín[3], Mafalda Dias[4], Jonathan Frazer[4], Rosalie Sterenborg[5], linda de rooij[6], anna dolcetta-capuzzo[6], alexander teumer[7], Marcel Meima[8], Marco Medici[9], juan pablo nicola[3], debora marks[4] & W. Edward Visser[10]
[1]Academic Center for Thyroid Diseases, Academic Center for Thyroid Disease, Department of Internal Medicine, Erasmus Medical Center Rotterdam, The Netherlands, Department of Internal Medicine, Rotterdam, Netherlands; [2]Erasmus MC, Academic Center for Thyroid Disease, Department of Internal Medicine, Rotterdam, Netherlands; [3]Departamento de Bioquímica Clínica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Córdoba, Argentina; [4]Department of Systems Biology, Harvard Medical School, Boston, MA, USA; [5]Academic Center for Thyroid Disease, Department of Internal Medicine, Erasmus Medical Center Rotterdam, The Netherlands, Department of Internal Medicine, Division of Endocrinology, Radboud University Medical Center, Nijmegen, The Netherlands, Netherlands; [6]Academic Center for Thyroid Disease, Department of Internal Medicine, Erasmus Medical Center Rotterdam, The Netherlands; [7]Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany, Dzhk (German Center for Cardiovascular Research), Partner Site Greifswald, Greifswald, Germany; [8]Dept of Internal Medicine, Academic Center for Thyroid Diseases, Erasmus MC, Rotterdam, Rotterdam, Netherlands; [9]Radboud University Medical Center, Nijmegen, Erasmus Medical Center, Rotterdam, Department of Internal Medicine, Radboud University Medical Center, Nijmegen, Netherlands; [10]Erasmus Medical Center, Academic Center for Thyroid Diseases, Department of Internal Medicine, Academic Center for Thyroid Diseases, Rotterdam, Netherlands

Background
MCT8 deficiency is caused by loss-of-function (LoF) mutations in thyroid hormone (TH) transporter MCT8. Patients have developmental delay and abnormal thyroid function tests (TFTs). The large phenotypic variability is not understood. Moreover, phenotypes arising from LoF mutations could be employed to enhance understanding of physiology in the general population. Also, computational disease variant classifiers have poor predictive power to ascertain impact of MCT8 variants. We conducted a generalizable approach that addresses all abovementioned challenges.
Methods
We systematically integrated genetic, clinical and biochemical data from 371 patients with MCT8 deficiency, accrued through combination of data from our well-phenotyped global cohort and meta-analysis of all reported cases. We assessed the impact of common genetic variation in MCT8 on TFTs in ~70k individuals. We evaluated impact of 108 patient mutations and 304 MCT8 variants in a full alanine-scanning by TH transport assays. We linked three distinct LoF classes (mild, moderate, severe) to phenotypic outcomes and mapped all variants onto our homology model. Utilizing these data and conservation analyses, an MCT8 deficiency-specific variant classifier was constructed using artificial intelligence methods.
Findings
Linking the different LoF classes to phenotypic outcomes, we observed a clear genotype-phenotype relationship across a range of disease features. Functional impact of variants strongly associated with survival of patients (median survival mild LoF: 71yrs; moderate LoF: 60yrs; severe LoF: 21.4yrs). Similar observations were noted for developmental (e.g. motor function), clinical (e.g. seizures) and biochemical (e.g. fT4, but not T3) features. Beneficial effects of the TH analogue Triac on several disease outcomes were independent of LoF category. By cross-referencing functional alanine-scanning data with patient mutants, we could infer the underlying mechanisms for the majority of variants. Our MCT8-specific classifier largely outperformed (AUC 0.95) commonly used prediction tools. Common genetic variation in MCT8 was associated with lower serum fT4, but not with TSH or T3 concentrations, resembling the genotype-phenotype relationships in patients.
Interpretation
The combination of deep phenotyping data from patients with MCT8 deficiency with a battery of functional and computational tests and with outcomes in population cohorts, enabled us to: (i) understand the divergent clinical phenotypes of MCT8 deficiency, (ii) assess therapy effectiveness, (iii) advance structural insights of MCT8, (iv) create a high-quality disease variant classifier, together also leveraging information on the role of MCT8 in non-affected individuals in the population.

DOI: 10.1530/endoabs.84.OP-11-58

Oral Session 12: Nodules and Diagnostic

OP-12-59

Autonomously functioning thyroid nodules present intermediate malignancy risk according to european thyroid imaging and reporting data system; a comprehensive clinical, cytological and molecular characterization

Aglaia Kyrilli[1], nunzia tacelli[2], Laetitia Lebrun[3], Isabelle Salmon[4], Gilles Russ[5], Rodrigo Moreno-Reyes[6] & Bernard Corvilain[7]
[1]Cliniques Universitaires de Bruxelles- Hôpital Erasme, Endocrinology, Brussels , Belgium; [2]Cliniques Universitaires de Bruxelles – Hôpital Erasme, Radiology, Brussels, Belgium; [3]Cliniques Universitaires de Bruxelles – Hôpital Erasme, Anatomopathology, Brussels, Belgium; [4]Hôpital Erasme, Anatomie Pathologique, Brussels, Belgium; [5]Thyroid and Endocrine Tumors, Institute of Endocrinology, Pitie Salpetriere Hospital, Sorbonne University, Paris, France; [6]Cliniques Universitaires de Bruxelles – Hôpital Erasme, Nuclear Medicine, Brussels, Belgium; [7]Cliniques Universitaires de Bruxelles – Hôpital Erasme, Hub-Erasme University Hospital, Université Libre de Bruxelles, Endocrinology, Brussels, Belgium

Objectives
To systematically characterize autonomously functioning thyroid nodules (AFTN) by clinical, biological and imaging methods, cytology and histology when indicated.