from 1981 to 2019 through the NHS Scotland Information Services Division after ethics approval. Controls were matched for age, birthweight, gestation and deprivation index. Incident admissions for angina, arrhythmia, diabetes, heart failure, ischaemic heart disease, myocardial infarction, peripheral arterial disease, renal failure and stroke were obtained for each individual. Case control analysis was performed using Chi square test using R. Results: Admission data on 13,481 men with hypospadias and 9,615 matched controls were reviewed. Men with hypospadias had a 10- fold higher risk of diabetes (9.7 [8.4-11.2], p<0.0001); 9- fold higher risk of ischaemic heart disease (OR [95% CI] 9.1[8.1-10.2], p<0.0001); 8- fold higher risk of renal failure (7.9 [6.9-9.1], p<0.0001); 6- fold higher risk of stroke (6.2 [5.2-7.2], p<0.0001); 6- fold higher risk of myocardial infarction (6.4 [5.6-7.3], p<0.0001); 6-fold higher risk of angina (5.9 [5.3;6.8], p<0.0001); 5-fold higher risk of arrhythmia (4.8 [4.2-5.4], p<0.0001) 5- fold higher risk of peripheral arterial disease (4.8 [3.7-6.1], p<0.0001) and 4- fold higher risk of heart failure (3.6 [3.1-4.1], p<0.0001). Conclusions: Men with a history of hypospadias are at significantly increased risk of admission for treatment for cardiovascular and metabolic conditions, especially ischaemic heart disease, diabetes and renal failure. The mechanisms underlying this observed increase are unclear and merit further evaluation.

Thyroid

THYROID HORMONE ACTION AND SIGNALING

Long-Term Efficacy of T3 Analogue Triac in MCT8 Deficiency

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OR01-05

Background: MCT8 deficiency is a severe disorder caused by mutations in the thyroid hormone transporter MCT8. MCT8 deficiency is characterized by severe intellectual and motor disability and high serum T3 concentrations that result in thyrotoxic symptoms in peripheral tissues. This predisposes to substantial morbidity and mortality. Preclinical studies showed that the T3 analogue Triac can bypass defective MCT8 at the cellular level. Recently, we reported the results of an international multicenter trial, in which biochemical and clinical outcomes improved in patients with MCT8 deficiency who were treated with Triac for 12 months (1). However, long-term follow-up data of patients with MCT8 deficiency treated with Triac are lacking, particularly in young children. Therefore, we aimed to investigate the long-term efficacy of Triac therapy in a worldwide cohort of patients with MCT8 deficiency.
Methods: We investigated the efficacy of oral Triac treatment in pediatric (n=78) and adult (n=5) patients with MCT8 deficiency in 20 countries. Triac dose was titrated according a predefined dose-escalation scheme aiming to normalize serum T3 concentrations (target 1.4-2.5 nmol/L). Thyroid function tests and biochemical markers of thyroid hormone action in peripheral tissues (SHBG, creatine kinase, creatinine) were measured at baseline and during control visits.
Findings: In total, 83 patients with a median baseline age of 5 years (range 6 months – 66 years) were treated, including 24 patients aged 0-2.5 years and 17 patients aged 2.5-5 years. They were treated with Triac during 144 patient years, of whom the follow-up time was >5 years in 9 patients and 2-5 years in 22 patients. Mean dose was 45 µg/kg/day (range 11-107 µg/kg/day). Once a stable dose was achieved, no further dose adjustments were needed.
Mean serum T3 concentrations decreased from 5.02 to 1.94 nmol/L (normal 1.4 – 2.5 nmol/L). SHBG concentrations improved from 238 to 204 nmol/L (normal 40-140 nmol/L). Mean creatine kinase and creatinine concentrations improved from 113 to 140 U/L (normal <230 U/L) and from 32 to 38 µmol/L (normal 31-68 µmol/L), respectively. No drug-related severe adverse events were reported.
Interpretation: Triac is a safe treatment that results in sustainable improvements of the severe thyrotoxic state in pediatric and adult patients with MCT8 deficiency.
References: 1. Groeneweg S, Peeters RP, Moran C, Stoupa A, Auriol F, Tonduti D, et al. Effectiveness and safety of the tri-iodothyronine analogue Triac in children and adults with MCT8 deficiency: an international, single-arm, open-label, phase 2 trial. Lancet Diabetes Endocrinol. 2019;7(9):695-706.

Steroid Hormones and Receptors

STEROID AND NUCLEAR RECEPTORS

Steroid Hormone Metabolism Mediated Racial Disparity in Men with Benign Prostatic Hyperplasia

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SUN-747

Introduction and Objective: Racial disparity in prostate cancer has been well established, with African American (AA) men having higher rates of diagnoses and death from the disease compared to Caucasian American (CA) men. AA men also have a high incidence of benign prostatic hyperplasia (BPH), a disease associated with lower urinary tract symptoms (LUTS) that affect >210 million men worldwide. Furthermore, AA men with BPH have an increased incidence of non-surgical treatment failure, larger prostates at time of surgery, and surgery occurring at a younger age. The use of selective estrogen receptor modulators (SERMs) in the treatment of BPH has been proposed, as an increase in ERα has been associated with disease progression. AA men have higher levels of circulating estrogens as compared to CA leading to an increased prenatal exposure to estrogens. Estrogen exposure has been shown to alter the epigenetic landscape of genes, and this prenatal exposure to estrogens could sensitize the AA men to altered steroid homeostasis leading to an increase susceptibility to BPH and an altered response to treatment. In this study, we examine the prostate expression and localization changes in estrogen receptors (ERα, ERβ) as well as steroid metabolism genes

in AA and CA with or without BPH. **Methods:** To examine the impact of race on BPH, we examined prostate tissue from 66 men. We utilized 21 normal transition zone controls from radical prostatectomies, 8 normal transition zone controls from organ donors, and 37 BPH samples divided between CA and AA men. Using multispectral quantitative multiplex IHC, we examined the steroid hormone related protein expression of ERα, ERβ, CYP7B1, and AKR1C1 on each FFPE tissue section. We quantified the optical density of each protein of interest as well as examined colocalization and coexpression through cell and tissue segmentation. **Results:** In CA men, there is a dysregulation of ERα:ERβ homeostasis with BPH relative to normal as an increase in ERα and a decrease in ERβ expression was observed. Furthermore, an increase in CYP7B1, an enzyme that degrades ERβ ligands, was also observed. In AA men, we observed no difference between normal and BPH states, however in both normal and BPH prostate tissues, ERα and ERβ were increased relative to CA men. In addition, there is a decrease in AKR1C1, the enzyme that metabolizes DHT to an ERβ ligand. **Conclusions:** Our study supports the concept that differences in hormone pathways exist between AA and CA men. Understanding how these racial difference in steroid metabolism enzymes as well as ERs between CA and AA men with BPH could enhance treatment strategies for men with BPH.

Neuroendocrinology and Pituitary

PITUITARY TUMORS I

CircVPS13c Promotes Tumor Growth and Invasiveness in Pituitary Adenoma by Downregulating IFITM1

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SAT-315

CircVPS13C promotes tumor growth and invasiveness in pituitary adenoma by downregulating IFITM1

Background and objectives

Invasive nonfunctioning pituitary adenoma (NFPA) remains the major cause of hypopituitarism and infertility. Increasing evidences suggest that circular RNAs (circRNAs) exert crucial functions in regulating gene expression in a wide range of tumors. The present study was designed to explore the role of circRNAs in proliferation and invasion of NFPAs.

Methods

The expression profile of circRNAs was compared with circRNA array between NFPA (n=10) and normal pituitary tissues (n=4), invasive (n=5) and noninvasive (n=5) NFPA samples. A total of 249 circRNAs were shown to be significantly upregulated in human invasive NFPA tissues, comparing to the noninvasive ones. CircVPS13C was identified for further study, whose oncogenic effect were explored with in vitro and in vivo experiments.

Results

CircVPS13C was markedly upregulated in NFPA samples and positively correlated with NFPA invasiveness. Silencing of circVPS13C effectively suppressed NFPA cell proliferation, invasiveness and promoted apoptosis, *in vitro*, and suppressed tumor growth, *in vivo*. The oncogenic effects were

significantly enhanced when circVPS13C was overexpressed. By whole exome sequencing, interferon induced transmembrane protein 1 (IFITM1) was found significantly increased in cells with circVPS13C knockout. Decreased level of IFITM1 protein was confirmed in NFPAs samples, and negatively correlated with the level of circVPS13C and tumor invasiveness. Upregulation of IFITM1 could partly reverse the effect of IFITM1 on tumor cells, and IFITM1 downregulating enhanced the oncogenic effect of circVPS13C. CHIRP analysis suggested that circVPS13C may inhibit the IFITM1 transcription by competitively binding the RNA-associated proteins.

Conclusions

CircVPS13C promotes NFPA growth and invasiveness by regulating tumor suppressor IFITM1, revealing a therapeutic target in preventing the tumorigenesis of NFPA.

Key words

Pituitary adenoma, Circular RNA, CircVPS13C, IFITM1

Diabetes Mellitus and Glucose Metabolism

CLINICAL AND TRANSLATIONAL GLUCOSE METABOLISM AND DIABETES

Difference in Risk Factors Between Adults with Early Onset (<40 Years Old) Versus Late Onset (≥40 Years Old) Diabetes Mellitus Type 2 at the University of Santo Tomas Hospital from January 2015-December 2017

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MON-634

INTRODUCTION: Diabetes will remain a threat to global health. The global burden of type 2 diabetes mellitus is significant and rising, with most of the increase occurring in the last two decades. While most of the rise in the prevalence of Type 2 diabetes mellitus occurs in the middle-aged and the elderly, it is becoming more common in younger patients. No longer just a disorder of mature age, there is now a well-recognized trend toward younger people presenting with the disease.

METHODS: This was a cross sectional study of medical records of adult patients at the University of Santo Tomas Hospital who met the inclusion criteria from January 2015 to December 2017. The subjects were divided into early onset (<40 years of age) and the late onset (≥40 years of age) group. Mean, standard deviation, counts and percentages were used to summarize data. The mean values of continuous variables between the two groups were analyzed using the independent sample t-test while categorical variables were analyzed using Chi square test. Logistic regression analysis was used to determine the association of age of onset and duration of diabetes to its complications.