important endocrine complication. The aim of this study is to determine the incidence of IH and characterise clinical presentation and outcomes in these patients.
Patients and Methods
We retrospectively evaluated consecutive adult patients with melanoma treated between December 2010 and August 2019 at a tertiary cancer centre. All patients received ipilimumab (3mg/kg) monotherapy or in combination with PD-1 (programmed cell death protein 1) inhibitors (nivolumab or pembrolizumab). Symptoms, pituitary hormone assessment, pituitary imaging and patient survival were assessed.
Results
Of 189 patients, 23 patients (12.2%, 13 male; age 59.2±11.8 years) presented with hypophysitis, two having received ipilimumab monotherapy. The median onset was at 17.3 weeks (range: 6.7-160 weeks) after treatment start, occurring in 57% after the fourth infusion (n=13). Five patients developed late-onset IH (range: 30.1-160 weeks) whilst on treatment with PD-1 inhibitors. Three of the patients developing hypophysitis (13%) received only a single ipilimumab infusion. Additional irAEs were diagnosed in 16 patients (70%) with IH, including six cases of destructive thyroiditis and one of autoimmune diabetes. The main presenting symptom of IH was lethargy (n=18, 78%) followed by headache (n=8, 35%). Corticotroph deficiency with cortisol levels <83 nmol/l (<3µg/dL) at presentation were observed in all patients. At diagnosis, a drop in cortisol level of >70% over a median time of 22 days (range: 3-39 days) was evident in 87% patients. A fall in fT4 level of at least 20% from baseline was observed in ten patients (59%, 10/17 – after excluding patients with thyroiditis) at a median of 4 weeks (range: 0-8 weeks) prior to the diagnosis of IH. Gonadotroph deficiency was detected in three male patients. At the end of follow-up (median 14.3 months, range: 1-61.5 months after IH diagnosis), corticotroph deficiency was persistent in all patients; seven of ten patients recovered thyrotroph function and gonadotroph deficit resolved in one patient. Three patients with hypophysitis died within the first year of immunotherapy.
Conclusion
The incidence of IH was 12.2%, predominantly occurring after the fourth infusion. IH is characterised by acute severe drop in cortisol levels to less than 3µg/dL. A falling fT4 may herald development of ACTH deficiency.

Neuroendocrinology and Pituitary

HYPOTHALAMIC-PITUITARY DEVELOPMENT AND FUNCTION

Musashi: A Novel Regulator of the Gonadotrope Transcriptome

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SAT-292
Sufficient nutrition is critical for reproduction. We have previously shown that leptin, a circulating indicator of fat stores, signals to pituitary gonadotropes to maintain gonadotropin releasing hormone receptor (GnRHR) protein levels in female mice. We hypothesized that this process is post-transcriptional, happening primarily through regulation of the RNA-binding protein Musashi (MSI). We showed that MSI binds to *Gnrhr* and inhibits translation, and a gonadotrope-specific deletion of *Msi1* and *Msi2* (Gon-*Msi1/2*-null) leads to *increased* GnRHR protein levels. This culminates in dysregulated luteinizing hormone (LH) and follicle-stimulating hormone (FSH). We have recently identified other gonadotrope and pituitary targets of MSI. We therefore suspected that MSI plays a role in both the maturation of gonadotropes and the normal cyclic regulation of gonadotropes. We hypothesized that the deletion of MSI would lead to downstream effects on (1) the composition of the gonadotrope population and (2) the molecular landscape of these cells. Using our adult, diestrous Gon-*Msi1/2*-null females, we performed single-cell RNA-sequencing on methanol-fixed dispersed pituitary cells. Libraries were made from two control pools and two mutant pools (n=3 pituitaries/pool) using 10x Genomics v3.1 Single-Cell Gene Expression technology and initially sequenced on an Illumina Next-seq mid-output flow-cell, yielding 5,000 reads/cell. Subsequent high-output sequencing obtained 25,000 reads/cell. We recovered single-cell mRNA transcript information from 18,206 control pituitary cells and 16,255 Gon-*Msi1/2*-null cells. Our analyses revealed that the Gon-*Msi1/2*-null pools had a higher % of cells expressing *Fshb*, as well as an expected significant drop in *Msi2*-expressing gonadotropes and no change in *Lhb*-expressing cells. We have recently identified *Fshb* as an MSI target *in silico*, and qRT-PCR of female pituitary lysate immunoprecipitated with anti-MSI1 shows a 7-fold enrichment in *Fshb* mRNA. We identified differentially expressed genes comparing the control and Gon-*Msi1/2*-null gonadotrope clusters. Using Gene Ontology analyses, the Gon-*Msi1/2*-null gonadotrope cluster appears to have aberrant expression of mRNAs involved in protein folding and cellular responses to nutrients. Our high-output sequencing has allowed us to achieve 25,000 reads/cell and will provide greater resolution of the role of Musashi in control of gonadotrope function. Taken together, our data indicate that Musashi influences the molecular landscape and subsequent physiology of the female gonadotrope. We have identified potential gonadotrope-specific MSI targets, including pathways that may underlie the dysregulated gonadotropin production and secretion seen in our Gon-*Msi1/2*-null females. Future studies will compare pubertal and adult females, as well as females from different estrous cycle stages.

Cardiovascular Endocrinology

HYPERTRIGLYCERIDEMIA; INFLAMMATION AND MUSCLE METABOLISM IN OBESITY AND WEIGHT LOSS I

Rare Case of Tocilizumab-Induced Severe Hypertriglyceridemia

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