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Primary Ovarian Insufficiency (POI) is a female fertility disorder which affects 1% of women before 40 years of age and manifests with amenorrhea, elevation of serum gonadotrophins and low estrogens. POI has a strong genetic component with incomplete penetrance. Several candidate genes have been described so far, however, its etiopathogenesis is mostly unknown. In order to discover the POI-related causative mechanisms, microarray transcriptome analysis in human granulosa cells (hGCs) stimulated with recombinant human BMP15 (rhBMP15) and next generation sequencing analysis (NGS) on the identified differentially expressed genes in a selected group of patients with POI were conducted on NGS Illumina platform. In the present study, we obtained 19 differentially expressed genes upon rhBMP15 stimulation in hGCs. **Results:** showed that all identified genes were upregulated and associated to pluripotency, inhibition of apoptosis, cell proliferation, BMP signaling and apoptosis. Moreover, we identified nine POI patients bearing six rare variants in 5 of the BMP15-induced genes (*SAMD11*, *SMAD6, ID1, USP35*, *GPCR137C*). The BMP15-induced transcriptome analysis in hGCs contributed the understanding of BMP15 role as transcriptional regulator, through the activation of transcriptional repressors, by inducing pathways inhibiting the ovarian follicle maturation, thus possibly maintaining an undifferentiated state of hGCs. These findings lead to the identification of novel candidate genes for POI.

Reproductive Endocrinology

OVARY, TESTES, AND IMPACT OF HORMONES ON METABOLIC FUNCTION

DHT Differentially Regulates T Helper Cell Related Cytokines and MicroRNAs In Visceral and Subcutaneous Adipose Tissue of Female Mice

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Hyperandrogenemic, insulin resistant polycystic ovarian syndrome (PCOS) patients often have low-grade inflammation due to elevated circulating pro-inflammatory markers. As up to 60% of PCOS patients are obese, whether this low-grade inflammatory state is due to increased adiposity or other factors such as hyperandrogenemia is unknown. Moreover, the systemic inflammation of obesity is correlated with recruitment of pro-inflammatory immune cell populations to WAT. We hypothesized that short-term administration of the potent androgen, dihydrotestosterone (DHT), to female mice would increase pro-inflammatory cytokines and microRNA (miR) associated with pro-inflammatory cytokines and immune cell populations in WAT. Sexually mature, normally-cycling female C57/Bl6 mice received a daily sc injection of oil (0 g; n=7) or DHT (27.5 g; n=7) beginning at estrus. Females had vaginal cytology daily. After three cycles or 12-16 days if mice became acyclic, mice were euthanized for collection of blood and WAT. Serum was analyzed for DHT and testosterone (TEST) by LC-MS/MS. TaqMan^{TM} Array Mouse Immune Response PCR assays (Thermofisher Scientific) were used to measure transcript expression levels in vWAT and scWAT. Ingenuity Pathway Analysis (IPA) (Qiagen) was used to analyze relationships between different transcript levels in each treatment group for each tissue. DHT mice had 17 fold higher serum DHT levels than oil mice but there was no difference in serum TEST between treatment groups. DHT mice had a significantly longer estrous cycle length then oil mice. Short-term administration of DHT significantly upregulated 23% (21 of 92) of transcripts in scWAT and downregulated 49% (45 of 92) of transcripts in vWAT. The top four canonical pathways identified by IPA in WAT were: T helper cell 1 (Th1), Th1 & T helper 2 activation, Helper T cell differentiation, and Altered B & T cell signaling. Based on the Th1 pathway derived from IPA, the following miRs (both -3p and 5p) downstream of Th1 activation targets were selected for qPCR in vWAT and scWAT: miR21, miR146a, miR29a, and miR155. Interestingly, miR-21a-5p, miR-146a-5p, and miR-155-5p were significantly upregulated in scWAT from DHT mice. No miRs were different between treatment groups in vWAT. We demonstrate for the first time that short-term DHT administration may cause immunosuppression in vWAT and inflammation, possibly mediated by miRs, in scWAT of female mice.

Reproductive Endocrinology

OVARY, TESTES, AND IMPACT OF HORMONES ON METABOLIC FUNCTION

Dietary Coconut Oil Mitigates Hyperandrogenemia in Obese Female Pigs Due to Suppression of Androgen Steroidogenesis in the Adrenal Cortex and