ISGE
GYNECOLOGICAL ENDOCRINOLOGY
THE 18TH WORLD CONGRESS
7-10 MARCH 2018 FLORENCE, ITALY

Genetic and epigenetic factors contributing to the hyperandrogenemia of PCOS

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Polycystic ovary syndrome (PCOS) is a multisystem disorder with a complex pathophysiology. Family-based studies, twin studies and genome-wide association studies (GWAS) indicate that there is a strong heritable component to the disorder. However, environmental factors are also known to influence the phenotype and there is recent interest in the potential role of epigenetic factors in the pathogenesis of PCOS. There has been particular interest in the role of microRNAs (miRNAs), which are epigenetic regulators that may bridge the genetic and epigenetic foundation of the disease. Several miRNAs, small, non-coding post-transcriptional gene regulators, are known to be differentially expressed in granulosa cells, follicular fluid, ovarian stroma, and in the circulation of women with PCOS. However, there are no reports on miRNA expression and target gene analysis in normal and PCOS theca cells, which are responsible for excess androgen levels that are the hallmark of PCOS. Understanding gene expression and its regulation in theca cells may represent a key to understanding the hyperandrogenemia of PCOS. Altered transcriptome profiles in theca cells, could be explained, at least in part, by miRNA regulation. We identified 18 miRNAs, which are differentially expressed in PCOS theca cells, some of which are predicted to target known PCOS candidate genes identified by GWAS. Using Ingenuity pathway analysis we identified a common network with ~45% of the differentially expressed miRNAs identified in this study, and 73% of the known PCOS candidate genes. Correlated expression patterns of some of these miRNA-target gene pairs were validated in vitro in theca cells, including hsa-miR-125a-3p targeting DENND1A.V2, which has a functional role in PCOS theca cell steroidogenesis. Our findings suggest that the PCOS candidate genes derived from GWAS are part of a complex network regulated by miRNAs. This suggests both genetic and epigenetic regulation of PCOS GWAS candidate gene transcription and augmented androgen biosynthesis in the PCOS ovary.

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