P-36 Transcriptional Profiling with a Pathway-oriented analysis Identifies Dysregulated Molecular Phenotypes of Endometrium in Patients of Polycystic Ovarian Syndrome

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Objectives: Polycystic ovary syndrome (PCOS) is the most common cause of anovulatory infertility affecting 5~10% of women of reproductive age. The common clinical manifestations are oligo-/amenorrhea, hirsutism, and often associated with obesity and insulin resistance/hyperinsulinemia. Patients with PCOS also have high risk of recurrent spontaneous abortion, endometrial hyperplasia and endometrial cancer, suggesting that PCOS could alter physiology of endometrium in these patients. However, the genome-wide molecular mechanisms by which PCOS affect endometrial homeostasis still remain unexplored. Thus, the objective of this study was to identify dysregulated signaling pathways in endometrium of patients suffering from PCOS by analyzing expression profiles with gene set enrichment analysis (GSEA), a knowledge-based supervised analysis method.

Methods: Endometrial tissues from PCOS patients and control healthy women were obtained and divided into two pieces for histological analysis and RNA preparation, respectively. In all tissue samples, histological dating and classification were evaluated by 2003 ESHRE/ASRM PCOS criteria. The control endometrium was selected in the proliferative phase because of the similar morphology of the proliferative endometrium with that of PCOS patients. Ultrasonogram was performed to examine the thickness of endometrium in all patients and endometrial tissues with 7~10 mm thickness were biopsied. Oligo microarrays with Affymetrix HG-U133A 2.0 containing ~22,000 human genes were performed and GSEA was applied to interpret expression profiles from the microarrays. Semi-quantitative and/or realtime RT-PCR was carried out with additional RNA samples to validate results from GSEA.

Results: GSEA provides a list of biological pathways aberrantly operating in the endometrium of PCOS patients (PCOSE). While 2 gene sets are significant at false discovery rate (FDR) <25% in PCOSE, 44 gene sets are significant at FDR <25% in control. This suggests that most dysregulated biological pathways in PCOSE are down-regulated. Crucial factors regulating cell cycle, such as MCMs and cyclins, are down-regulated in PCOSE. mRNA expression of enzymes involved in glycolysis is coordinately down-regulated in PCOSE, suggesting that glucose metabolism in endometrium affected by PCOS is significantly altered. Semi-quantitative and quantitative RT-PCR validated that most of genes working for glycolysis are systematically down-regulated in PCOSE. Integrin-Rho-cytoskeleton networks are coordinately down-regulated in endometrium of PCOS patients as well.

Conclusion: A pathway-oriented computational analysis, such as GSEA, for genome-wide expression profiles provides an insight for appreciating molecular abnormalities that reflect pathogenesis of PCOS, possibly leading to increased risks at spontaneous pregnancy loss and endometrial carcinoma.