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A SYSTEMIC REVIEW ON DIFFERENTIAL REGULATION OF GENES IN POLYCYSTIC OVARIAN SYNDROME DISEASE

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ABSTRACT

Polycystic ovary syndrome (PCOS) is one of the common endocrine disorders among women of reproductive age with a prevalence of approximately 5–-10% worldwide. PCOS is a common reproductive disorder characterized by arrested follicular development prior to selection of a dominant follicle. Our aim is to explore the available literature on PCOS and associated genes to study the effect of differential regulation of genes and the role of miRNAs in PCOS condition. In this paper, we have presented comprehensive information on the association between PCOS and candidate genes based on the literature survey. We have evaluated the association at various levels, including genes that are upregulated and downregulated in PCOS and the associated effects of dysregulation of genes in PCOS. The detailed literature study revealed the association of differential expression of genes and its critical effect in PCOS, including endometrial receptivity, implantation failure, early pregnancy loss, pre-term birth, insulin resistance, and hyperandrogenim.

KEYWORDS: **PCOS; Polycystic Ovarian Syndrome; Gene Regulation; Gene Expression**

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a complex disorder affecting approximately 5–10% of all women of reproductive age[1]. It is a multifactorial endocrine disorder, which demonstrates menstrual disturbance, infertility, anovulation, hirsutism, hyperandrogenemia/hyperandrogenism[2].
PCOS is a common reproductive disorder characterized by arrested follicular development prior to selection of a dominant follicle. The increase in the secretion of androgens by the ovaries and the adrenal glands is one of the pathological effects observed in PCOS[3]. PCOS is also associated with an increased risk of developing Type 2 diabetes, dyslipidemia, and cardiovascular diseases[4]. Insulin resistance, a common disorder associated with PCOS, is as high as upto 70% in PCOS condition [3]. The etiology of PCOS is still unclear; however, it has been observed that various environmental factors, genetic factors, including genetic variations, differential regulation of genes, affected pathways, may contribute to the pathogenesis of PCOS [4]. Women with PCOS are also at an increased risk of developing gestational diabetes and pre-term birth (PTB) [5, 6]. It has also been observed that the pregnant women diagnosed with PCOS are likely to give birth to premature babies [5]. Although various gene expression studies have been done in PCOS, the information is scattered in the literature, which is the most specific challenge for the researcher. In this review, we have attempted to assemble the information on differential regulation of genes in PCOS, through comprehensive literature study. Based on the literature survey, we have evaluated the association of differential regulation of genes at various levels, including genes that are upregulated and downregulated in PCOS and the associated effects of dysregulation of genes. The differential expression of genes involved in the androgen biosynthesis, angiogenesis, follicular development, and at different stages of the embryonic development, contributes to the various phenotypes associated with PCOS[7, 8]. In this review, we have underpinned the various changes at the molecular level, including the differential expression of genes and miRNAs in the PCOS and its serious effects, including endometrial receptivity, implantation failure, early pregnancy loss, PTB, insulin resistance, hyperandrogenesim in women with PCOS[9, 10].

MATERIALS AND METHODS

Search Strategy

('PCOS' or 'Polycystic Ovary Syndrome' or PCOS) AND 'Gene' was used a keyword in PubMed Medline Database to search for the papers. References were screened at the abstract level to segregate the false positive papers from the hit list. All potential published studies on candidate genes and PCOS were identified through different databases and evaluated. The true positive papers werecollected to perform the manual data extraction process.

Data extraction

Manual curation process was adopted to extract the information. All papers were read, and specific information on PCOS, Associated genes, Mechanism of Association, Significance of Association, Drugs if mentioned were carefully captured from the papers according to the authors' interpretation of the results.

RESULTS AND DISCUSSION

Differential regulation of genes in PCOS

Gene expression is the most fundamental level at which the genotype gives rise to the phenotype. Altered gene expression plays a major role in the pathogenesis as well as susceptibility to PCOS. Several studies served as evidence in this matter. An increase in the concentrations of Follistatin with the decrease in the concentrations of Activin found to be associated with the arrest of follicular development not proceeding beyond 8–10 mm and may also be partially responsible for the lack of pre-ovular follicle development in PCOS [11].The relation between high follistatin and low

activin. A serum concentration was found to contribute to the pathophysiology of PCOS [12].Proteomic studies revealed that the proteomic biomarkers, such as Pyruvate kinase M1/M2, Vimentin, Fructose bisphosphonate aldolase A, Heat shock protein beta-1, Peroxiredoxin-1, and Transferrin, were found to be differentially expressed in women with PTB and PCOS [13].The expression of Prostatic-specific Antigen (PSA) gene was found to be higher in PCOS condition, and this might also be used as a diagnostic criterion for hirsutism, as the free PSA levels were found to be higher in women suffering from hirsutism and PCOS [14]. The Bone Morphogenetic Proteins (BMP) were found to be involved in the reproductive abnormalities associated with PCOS, overexpression of BMP6, and BMPR1A was observed in granulosa cells from PCOS women[15].The decrease in the expression of CD36 (Scavenger receptor gene) was associated with the increase in the levels of Testosterone and Insulin in follicular fluid and observed to play a role in the pathogenesis of PCOS [16]. The increased androgen production in PCOS was correlated with the increased levels of steroidogenic enzymes, CYP17, and CYP11A observed in PCOS theca cells. In addition, the transcription factor GATA6, which regulated the promoter activity of CYP17 and CYP11A,was also found to be overexpressed in PCOS [17].Another study showed that the abundance of CYP11A1 mRNA in PCOS increased the CYP11A1 promoter activity and also increased the stability of CYP11A1 mRNA in PCOS condition [18]. Although the overexpression of CYP17 and CYP11A mRNA were observed in theca cells from polycystic ovaries, further investigation to correlate the polymorphic differences in the genes to the increased expression levels revealed that no significant dose effects of the CYP17 and CYP11A alleles were observed [19]. The study on the association of MAPK (Mitogen activated protein kinase) signaling in androgen synthesis and CYP17 gene expression in PCOS revealed that reduced MEK1/2 phosphorylation was found in PCOS which was directly associated with the increase in CYP17 accumulation and DHEA (dehydroepiandrosterone) abundance in PCOS condition. Similarly decreased ERK1/2 phosphorylation in PCOS was directly associated with the increased CYP17 promoter activity, DHEA abundance, and increased levels of CYP17 in PCOS [20].The study on different effects of retinol and retinoids in PCOS condition revealed an increased expression of Dehydroepiandrosterone and Testosterone in PCOS theca cells, and it has been found that retinoids stimulated CYP17 abundance and increase in the promoter activity of CYP17 in PCOS theca cells, suggests that the altered retinoic acid synthesis may be involved androgen production and CYP17 gene expression in PCOS [21]. The enzyme P450c17 played a critical role in the regulation of androgen synthesis. It has been observed that the activity of P450c17 was stimulated by Insulin/IGF system within the ovaries and adrenal glands. The dysregulation of the enzyme P450c17 was a significant factor in the hyperadrogenism of PCOS [22]. Aromatase mRNA expression has been studied in the individual follicles from PCOS patients, and the data indicatedthat all follicles in PCOS contained decrease in the levels of P450AROM, Estradiol, and Aromatase-stimulating bioactivity. The low production of Estradiol in PCOS follicles was directly correlated to the insufficient aromatase-stimulating bioactivity, which was necessary to increase P450AROM mRNA expression [23].The p160 family of steroid receptor coactivators, AIB1 (amplified in breast cancer-1), transcriptional intermediary factor-2, were found to be overexpressed in the endometrium of women with PCOS, which was associated with the endometrium sensitivity to estrogen that may correlate with the increased incidence of endometrial hyperplasia and cancer in women with PCOS [9].Oocyte-derived growth factor, GDF-9 (Growth Differentiation Factor-9) was critical for normal folliculogenesis and female fertility, the level of GDF-9 was found to be decreased in PCOS condition, suggested that dysregulation of GDF-9 in PCOS women may contribute to abnormal folliculogenesis [24]. Increased expression of HOXA10 (Homeobox A10) in the endometrium was crucial for embryo implantation. Endometrial receptivity was

assessed in PCOS condition by determining the effect of increased ovarian androgens. Increased expression of Testosterone, a novel regulator of HOXA10, was found to suppress the expression of HOXA10 and by diminishing the reproduction potential of women with PCOS[10]. GLUT4 (insulin-sensitive glucose transporter) was significantly lower in PCOS women and patients with Insulin Resistance [25]. The expression of 11β-hydroxysteroid dehydrogenase (11β-HSD1) mRNA was investigated in obese women with PCOS, which indicated highly elevated levels of 11β-HSDB1 in the subcutaneous adipose tissue that may correlate with the increased cortisol, affecting the secretion of the local adipose tissue associated with Obesity [26]. Intrafollicular insulin-like growth factor (IGF) levels were studied in PCOS condition. The results indicated that IGF-II was significantly lower in PCOS, and in addition, differential expressions were observed in IGF1, EGF (Epidermal growth factor), inhibin, and TGF beta concentrations in PCOS condition [27] Abnormal expressions of genes were identified in non-obese PCOS adipose tissue. Inflammatory response genes were significantly downregulated that included the decreased expression of Interleukin 6 (IL6), chemokine (C-X-C motif) ligand 2 (CXCL2), and Suppressor of cytokine signalling 3 (SOCS3)[28]. The results also indicated that Lipid metabolism genes such as Dehydrogenase/reductase member 9 (DHRS9), ubiquitin carboxyl-terminal esterase L1 (UCLH1), and fatty acid desaturase 1 (FADS1), with insulin resistance, were significantly overexpressed in PCOS condition. Some of the genes involved in the Wnt signalling pathways,dickkopf WNT signaling pathway inhibitor 2 (DKK2), jun proto-oncogene (JUN), FOSB, were differentially expressed in PCOS [28]. The expression of inhibin subunits alpha, beta A, and beta B mRNAs have been regulated differently in human follicular granulosa and theca cells in PCOS condition, which caused an assumption speculation that inhibin may be involved in the development of PCOS; however, the results showed that the inhibin subunit mRNAs was not disturbed in PCOS ovaries [29]. The study of the expression of steroid receptors, coactivators, and regulators associated with endometrial receptivity in untreated PCOS patients indicated increased expression of Estrogen receptor alpha and coactivators ARA70. In contrast, the expression of beta3-integrin in the epithelia was found to be lower in PCOS, which partially explainedthat the reduced level of beta3-integrin was associated with implantation failure in untreated PCOS patients [30]. Gene expression profiling of Cucumuls Cells (CCs) in PCOS revealed differential expression of LHCGR, ANGPTL1, TNIK, GRIN2A, SFRP4, and SOCS3, and the same was confirmed by RT-PCR, and LHCGR, TNIK, and SOCS3 were found to be associated with embryo development to blastocyst stage that made these genes as candidate markers for the embryo viability in PCOS patients[31]. 5alpha-reductase activity, associated with the follicular development,has been studied in PCOS patients in both granulosa and theca cells. An elevated level of 5alpha-Reductase 1 and 2 has beenobserved in both the cells, and the results showed that 5alpha-reduced androgens may play a role in the pathogenesis of PCOS [7].Transforming growth factor beta (TGF-β) was found to be differentially regulated in PCOS. Genetic variation in Fibrillin 3 protein, the regulator of TGF-β signaling,has beenassociated with the differential regulation of TGF-β. The dysregulation of TGF-β may contribute to reproductive abnormalities, cardiovascular, and metabolic abnormalities in PCOS [32]. Angiogenic factor genes like Vascular endothelial growth factor (VEGF), Endocrine Gland derived (EG)-VEGF,were found to be differentially expressed in PCOS ovaries, however in different cell types and at different cell differentiation stages. Increased expression of EG-VEGF was found in theca interna and stroma cells, which was related to the new blood vessels, and the expression VEGF mRNA was predominately associated with granulosa cells suggesting its role in both angiogenesis and possibly cyst formation[33].DENND1A.v2 (DENN/MAD domain containing 1 A, Variant 2), an isoform,was highly expressed in PCOS theca cells, and exosomal DENND1A.v2

was significantly increased in urine from PCOS women. Knockdown of DENND1A.v2 in PCOS theca cells decreased the androgen biosynthesis of CYP17A1, and CYP11A1 in PCOS condition, which suggested the key role of DENND1A.v2 in hyperandrogenemia associated with PCOS [8]. Epithelial Na(+) channel (ENaC) (γ-ENaC) was found to be downregulated in PCOS. High serum leptin may reduce endometrial receptivity by activating the STAT3 signal pathway and downregulating γ-ENaC expression in the endometrium, resulting into linking abnormal ENaC gene expression to early pregnancy loss in obese PCOS patients [34].The novel adipokines TWIST1 and HMOX1 were found to be differentially expressed in PCOS, correlated with Body Mass Index (BMI) and Glucose infusion rate (GIR). The levels of adiponectin receptor 2 (ADIPOR2), LPL, and TWIST1were decreased, while the expression of chemokine (C-C motif) ligand 2 (CCL2) and heme oxygenase (decycling 1) (HMOX1) was increased [35].

Role of microRNAs in PCOS

MicroRNAs (miRNAs) are short RNA molecules which bind to target mRNAs and regulate gene expression at the post-transcriptional level. Understanding of miRNAs in relation to PCOS is at an early stage. Some of the recent findings demonstrated the role of miRNAs in PCOS. GLUT-4, highly predicted target for miR-93, a member of microRNA precursor miR-17 family,has been found to be regulating the gene GLUT4 (insulin-sensitive glucose transporter), which significantly lower in PCOS women and patients with Insulin Resistance[36]. Increased expression of miR-93 resulted in the decreased expression of GLUT4, whereas the inhibition of miR-93 found to upregulate the expression of GLUT4 which demonstrated the role of miR-93 in PCOS associated with Insulin Resistance[36]. Although miR-133 and miR-223 are found to be differentially regulated, its role in PCOS is yet to be defined [36]. Expression of circulating miRNAs is altered in obese patients with PCOS. miRNA-21, miR-27b, miR-103 are found to be increasingly expressed in obese women with PCOS, whereas it is reduced in obese women without PCOS, which suggested that miRNA regulation is influenced by obesity and circulating androgen concentrations[37]. Expression of cell-free miRNAs in the human follicular fluid revealed the role of miR-132, miR-320, miR-520c-3p, miR-24, and miR-222 in regulating the estradiol concentrations and showed the reduced levels of miR-132 and miR-320 in PCOS patients[38].

CONCLUSION AND FUTURE PERSPECTIVES

In summary, although the etiology of PCOS is still unclear, the pathology of PCOS can be associated with the macro and micro environmental factors. The differential regulation of genes plays an important role in the pathogenesis of PCOS as it is associated with various other endocrine disorders including diabetes, insulin resistance, cardiovascular diseases, hyperandrogenism, reproductive disorders, etc. The underlying mechanism and the network help in identifying the candidate genes or biomarkers that are dysregulated in the disease conditions. The next step of this research is to study the genetic variations involved in the PCOS condition across different population and ethnicities and to publish the results to the scientific community in the form of searchable relational database.

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