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Computational Systems Biology Approach on Polycystic Ovarian Syndrome (PCOS)

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Abstract

Polycystic ovarian syndrome (PCOS) is an endocrine disorder that affects women at reproductive age. This syndrome gives rise to various consequences, from reproductive, dermatological, nervous and psychiatric problems to different features of metabolic syndrome. Due to the complexity of PCOS, candidate gene approaches are insufficient to understand its molecular mechanism. A systems biology approach that requires strong integration of experimental and computational biology to understand the complex biological systems could be used in examining multiple interacting genes and their products that lead to PCOS. This short communication discusses the available omics studies that have been conducted in PCOS.

Keywords: Polycystic ovarian syndrome; Computational systems biology; Pathway construction; Omics data integration; Network analysis

Introduction

Polycystic ovarian syndrome (PCOS) is a complex disorder diagnosed by a combination of at least two out of three of these features; i.e., hyperandrogenism (excess of androgen or male hormone; such as hirsutism, hyperandrogenaemia), ovulatory dysfunction (including menstrual disturbance such as amenorrhea and oligomenorrhea) and presence of polycystic ovarian morphology (existence of excessive preantral follicles in the ovary) [1]. The diagnostic features of PCOS are heterogeneous as they can give rise to four different phenotypes (Figure 1). Approximately, globally about 5-20% women of reproductive age are affected by PCOS, possibly making this disorder the most hormonal disorder [2]. Despite the increased prevalence of PCOS, the mechanisms involved in its pathogenesis and pathophysiology are not completely understood. However, multiple factors are considered to be involved in the pathology process of PCOS including genetics, lifestyle and environment. Women with PCOS have an increased risk of developing other chronic problems such as type-2 diabetes mellitus, cardiovascular diseases, endometrial cancer and mental disorders [3].

The heterogeneity and complexity of PCOS resist traditional approaches that have been applied in identifying a single gene or pathway to understand the disease. PCOS might not be attributed to the perturbation of a single protein but caused by complex interactions among multiple proteins. Various studies have identified many candidate genes, proteins and metabolites involved in the pathogenesis of PCOS using different types of approach such as genomics, transcriptomics, metabolomics and bioinformatics [4-7].

Genomics is a study of structure, function and expression of the genes in an organism, and is one of the approaches that has been used to understand the molecular basis of PCOS. Two studies have identified eleven susceptible loci in Han Chinese population that are associated with PCOS [4,8]. Of the eleven, three loci associated with FSHR, LHCGR and THADA were identified in 2011 and the remaining eight (DENND1A, INSR, YAP1, C9orf3, RAB5B, HMGA2, TOX3 and SUMO1P1/ZNF217) were identified in 2012 [4,8]. Both studies demonstrated those loci were enriched with candidate genes that are related with biological mechanisms of PCOS such as insulin signaling, sex hormone function and type-2 diabetes mellitus.

On the other hand, a transcriptomics approach, which is a study of mRNA expression in a cell or tissue of an organism, has also been widely applied to profile the expression changes in PCOS. Majority of transcriptomic studies in PCOS used expression profiling by microarray. 30 transcriptomic studies of mRNA expressions in PCOS have been published between 2003 and 2015 [5,9-11]. Those studies identified differentially expressed mRNA in various cells and tissue in healthy and PCOS patients and novel genes responsible in the pathogenesis of PCOS were successfully identified. This new information provides new insights into the mechanism of PCOS.

Other than genomics and transcriptomics, proteomics is another method that was used to identify list of proteins towards understanding the molecular basis of PCOS. Currently 13 studies have utilized proteomic approach to profile the protein expression in multiple cells and tissues in normal and PCOS patients where they used 2D-PAGE or 2D-DIGE as an analytical method and mass spectroscopy to identify the proteins [12-15]. Unlike genomics and transcriptomics, the proteomics data that have been generated could be used to determine novel biomarker and to gain mechanistic insights on PCOS.

While genomics, transcriptomics and proteomics track the global expression of genes and proteins, metabolomics focuses on profiling, characterizing and quantifying the metabolites, which are mediators and products of metabolism [16]. In PCOS, eight metabolomic studies have compared the metabolites profiling between controls and PCOS patients. These studies were performed by analyzing the plasma or urine samples in either ^{1}H NMR, gas chromatography mass spectrometry (GC-MS), high-performance liquid chromatography-mass spectrometry (HPLC-MS/MS) or ultra-performance liquid

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Platform	Description	Example	References
Genomics	To identify the genetic evidences in PCOS	Identified eleven new risk loci in Han Chinese PCOS women	[4,8]
Transcriptomics	To identify differential expressed genes between non-PCOS and PCOS women	243 differential expressed genes were identified in the granulosa cells between non-PCOS and PCOS patients	[5]
Proteomics	To identify significant proteins expressed in PCOS women	Identified 186 proteins in follicular fluid of non-PCOS and PCOS women	[17]
Metabolomics	To detect altered metabolites in PCOS women	Altered metabolites in sera of PCOS women revealed disruptions in steroid hormone biosynthesis, amino acids and nucleotides metabolism, glutathione metabolism, as well as lipids and carbohydrates metabolism	[18]
Bioinformatics	To predict the mechanisms of PCOS by integration of previous experimental results using bioinformatics tools	Several biological processes such as insulin receptor signaling pathway and steroid biosynthesis were found to be involved in PCOS by integration of previous transcriptomics results with a protein network	[7]

Table 1: Omics approaches in PCOS.

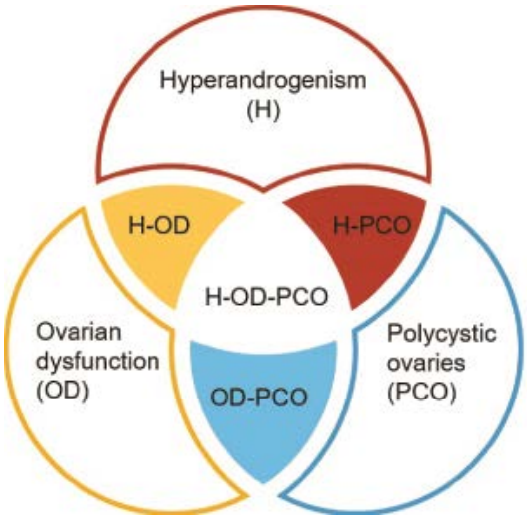

Figure 1: Four phenotypes based on three diagnostic features of PCOS. Current sets of diagnostic features give rise to a different number of PCOS phenotypes i.e., Type A: Hyperandrogenism, ovarian dysfunction and ultrasonographic appearance of polycystic ovaries; Type B: Hyperandrogenism and ovarian dysfunction; Type C: Hyperandrogenism and polycystic ovaries; Type D: Ovarian dysfunction and polycystic ovaries.

chromatography coupled with mass spectrometry (UPLC-MS/MS) [6,16]. The altered metabolites were found to be mostly involved in the carbohydrate, lipid and amino acid metabolisms [6,16].

Computational systems biology is used to analyze and integrate the data generated by experimental approaches and made available in the databases and various publications. In PCOS, among the earliest study that used computational approach was published in 2009, where they constructed the protein network from seven transcriptomics data to obtain a clearer view on the mechanism of PCOS [17,18]. This study has successfully identified one hypothetical protein, C1orf123 and a number of ontologies that are likely to be involved in PCOS. All omics approaches used in PCOS were summarized in Table 1.

Discussion

PCOS is a complex disorder (1) as its diagnostic features are not uniform (2), it manifests different symptoms in PCOS women and (3) could give rise to a variety of concurrent health problems. Besides, the treatment of PCOS is not specific and most of the drugs used to treat PCOS are palliative, drug that merely treats the symptoms rather than targeting responsible genes or pathways. The main reason for this lack of success is due to the complex genotype-to-phenotype relationship among the disease and associated genes or proteins [19].

According to all omics approaches used to study PCOS, each field could contribute towards significant knowledge in PCOS. Nevertheless, current findings that used the mentioned methods are insufficient to understand the pathogenesis of PCOS. The heterogeneity and complexity of PCOS might require combination and integration of different omics level (genomics to metabolomics) using computational approach.

In our research, we have successfully compiled all genes and proteins from previous published studies and public diseases databases. All data were stored in PCOSBase [20]. We combined all related pathways with the genes and proteins to construct a specific PCOS pathway network. Based on the PCOS pathway network, the interaction of metabolites that has been previously identified can be found. We have also integrated PCOS-associated diseases information into PCOS pathway network to uncover the mechanistic relationships between PCOS and other diseases. This study ultimately provides the interaction of molecules that have been experimentally identified and the association of other diseases with PCOS. Further analysis has been conducted to observe the association between PCOS and other diseases by extracting the information from the network to perform a comprehensive analysis on the association between PCOS and type-2 diabetes mellitus.

Conclusion

PCOS has been actively discussed for more than 80 years. Many efforts have been made to understand the etiology of PCOS. The presentation of multiple aspects of PCOS pathophysiology, combined with the computational approaches might be a valuable advantage in deciphering the mechanisms and the relationships involved in this syndrome. Integrated analysis of available experimental data, along with available human biological networks data and PCOS co-morbidities data can provide great prospects in identifying causative pathways and mechanisms that promote the occurrence of PCOS, as well as determining the striking similarities in the pathophysiology of PCOS and its related disorders. Moreover, this analysis may identify common molecular components and patterns responsible for PCOS and other diseases. It is hoped that new knowledge derived from the integration of experimental and computational approaches may in turn lead to novel therapeutic strategies for this devastating syndrome.

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