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Review

Proteomic and metabolomic approaches to the study of polycystic ovary syndrome

María Insenser, Rafael Montes-Nieto, Mora Murri, Héctor F. Escobar-Morreale *

Diabetes, Obesity and Human Reproduction Research Group, Hospital Universitario Ramón y Cajal, Universidad de Alcalá, E-28034 Madrid, Spain
Instituto Ramón y Cajal de Investigación Sanitaria IRYCIS, E-28034 Madrid, Spain
Centro de Investigación Biomédica en Red Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), E-28034 Madrid, Spain

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ABSTRACT

Polycystic ovary syndrome (PCOS) is considered a complex multifactorial disorder resulting from the interaction of genetic, environmental, and lifestyle influences. Nontargeted proteomics and metabolomics have been used in the past years with the aim of identifying molecules potentially involved in the pathophysiology of this frequent disorder. The biomolecules identified so far participate in many metabolic pathways, including energy metabolism (glucose and lipid metabolism), protein metabolic processes and protein folding, cytoskeleton structure, immune response, inflammation and iron metabolism, fibrinolysis and thrombosis, oxidative stress and intracellular calcium metabolism. These molecules provide key information about molecular functions altered in PCOS and raise questions concerning their precise role in the pathogenesis of this syndrome. The biomolecules identified by nontargeted proteomic and metabolomic approaches should be considered as candidates in future studies aiming to define specific molecular phenotypes of PCOS.

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1. Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders, affecting approximately 6–7% of women of childbearing age (Asuncion et al., 2000; Azziz et al., 2004; Carmina and Lobo, 1999; Moran et al., 2010; Sanchon et al., 2012). The diagnosis of PCOS relies on the association of clinical and/or

Abbreviations: PCOS, polycystic ovary syndrome.

* Corresponding author. Address: Department of Endocrinology, Hospital Ramón y Cajal & University of Alcalá, Carretera de Colmenar, km 9'1, E-28034 Madrid, Spain. Tel./fax: +34 91 3369029.
E-mail address: hescobarm.hrc@salud.madrid.org (H.F. Escobar-Morreale).

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biochemical hyperandrogenism with chronic oligo-anovulation and/or polycystic ovarian morphology, after the exclusion of specific etiologies (Azziz et al., 2006). Aside from symptoms of androgen excess and reproductive consequences, PCOS associates long-term risk factors for the development of severe metabolic disorders including obesity, diabetes and cardiovascular disease (Alvarez-Blasco et al., 2006; Escobar-Morreale and San Millan, 2007; Wild et al., 2010).

The pathogenesis of PCOS is complex and its etiology remains unclear. Androgen excess is a primary defect leading to PCOS (Wickenheisser et al., 2006) and, accordingly, PCOS is currently considered a mainly hyperandrogenic disorder (Azziz et al., 2006). Many patients with PCOS are overweight or obese (Carmina et al., 2007; Gambineri et al., 2002) and a predominantly abdominal distribution of body fat is particularly frequent in these women (Borruel et al., in press; Escobar-Morreale and San Millan, 2007). Moreover, insulin resistance is common in both obese and lean women with PCOS (Escobar-Morreale and San Millan, 2007) and 50–70% of patients with PCOS have insulin resistance and compensatory hyperinsulinism (Gambineri et al., 2002).

To explain the association of androgen excess, abdominal adiposity, insulin resistance and metabolic derangements in women with PCOS, we proposed the existence of a vicious circle in these women, that may start during early stages of life or even prenatally, whereby androgen excess favoring the abdominal deposition of fat further facilitates androgen secretion by the ovaries and adrenals in PCOS patients (Fig. 1) (Escobar-Morreale and San Millan, 2007). The facilitation of androgen secretion by abdominal adiposity is mediated through the effects of several mediators secreted by adipose tissue that may favor androgen secretion directly or through the induction of insulin resistance and compensatory hyperinsulinism (Nahum et al., 1995; Tosi et al., 2009).

Heterogeneity is an intrinsic characteristic of PCOS, from its definition to its phenotype, and is also present in the mechanisms leading to its development: the relative contributions of androgen excess and other factors to the development of PCOS in the individual patient are also heterogeneous. We explain PCOS as the result of a primary defect in steroidogenesis that leads to androgen excess of variable severity (Fig. 2) (Escobar-Morreale and San Millan, 2007). In some patients the defect is severe enough to result in PCOS without the participation of any other contributing factor. In others, a very mild defect in steroidogenesis is triggered by obesity, abdominal adiposity and insulin resistance, and the complete PCOS phenotype only develops when these factors are present. Between the two extremes there is a spectrum in the severity of the defect in androgen secretion, explaining the heterogeneity in the relative contribution of obesity and insulin resistance to the PCOS phenotype.

From an evolutionary perspective PCOS appears to be the result of the interaction of predisposing and protective genetic variants that may have provided survival advantage during times of stress and famine, with environmental factors such as life-style, diet and exercise that are heavily dependent on ethnicity (Escobar-Morreale et al., 2005a). However, our current understanding of the genetic, molecular and cellular mechanisms underlying PCOS is quite limited, in spite of considerable research efforts (Escobar-Morreale et al., 2005a; Simoni et al., 2008). The fact that most of this unsuccessful research efforts targeted specific proteins and genes based on previous knowledge about their role in certain disorders and metabolic and signaling pathways related to PCOS prompted a shift towards the application of nontargeted approaches to the study of this prevalent disorder.

The development and implementation of nontargeted high-throughput technologies, namely *omics*, might identify novel candidate molecules, which whose participation in the pathogenesis of PCOS could have not been suspected because of previous knowledge on the issue. Identification of such molecules, aside from providing new insights on PCOS, may even lead to the development of more precise diagnostic techniques and the identification of new therapeutic targets.

The contributions of genomics (genome-wide association studies) and transcriptomics (gene arrays) to the study of PCOS have been reviewed recently in this journal (Kosova and Urbanek, 2013). Therefore, the present review focuses on recent studies that

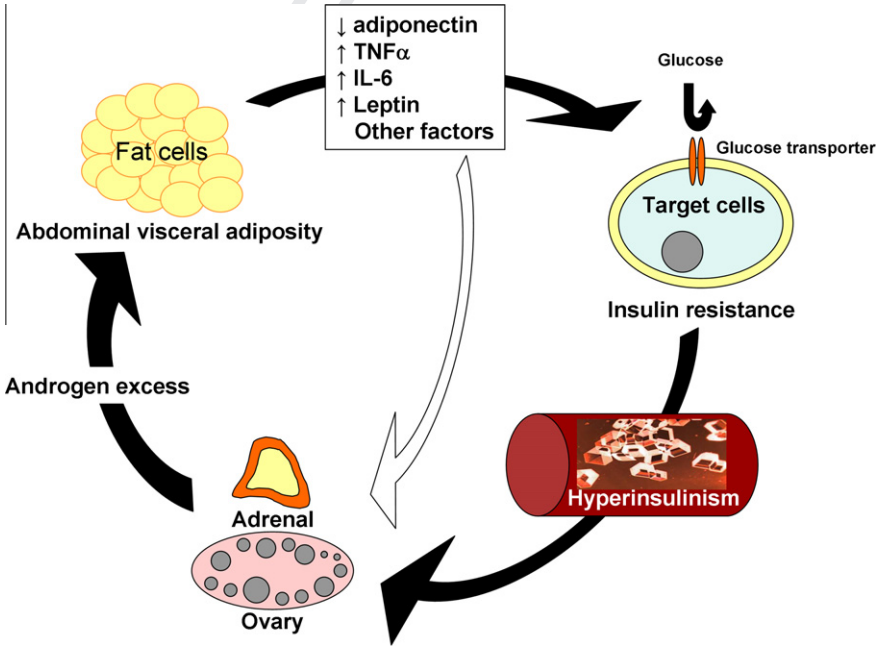

Fig. 1. Polycystic ovary syndrome and abdominal adiposity as the result of a vicious circle represented by the black arrows: androgen excess favors the abdominal deposition of body fat, and visceral fat facilitates androgen excess of ovarian and/or adrenal origin by the direct effects (white arrow) of several autocrine, paracrine and endocrine mediators, or indirectly by the induction of insulin resistance and hyperinsulinism. Reproduced from Escobar-Morreale and San-Millán (Escobar-Morreale and San Millan, 2007), with permission. Copyright Elsevier, 2007.

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