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Commentary

PGK1-AR axis: Benefits of a novel actor in PCOS pathology

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Polycystic ovary syndrome (PCOS) is a common endocrine and metabolic disorder amongst women of reproductive age [1]. The National Institutes of Health (NIH) estimates that cases of PCOS have tripled in the last 25 years, affecting one out of ten women worldwide [2]. Symptoms include menstrual irregularities, hyperandrogenism, disordered folliculogenesis, multiple small subcapsular cystic follicles, chronic anovulation, and infertility [1]. Besides reproductive abnormalities, PCOS is strongly associated with a large series of other disorders, including obesity, insulin resistance, dyslipidaemia, cardiovascular diseases, chronic low-grade inflammation, type 2 diabetes mellitus, hirsutism, alopecia, skin tags, acne, and psychological disturbances [1]. Consequently, PCOS is now a growing global public health issue, and its prevention and management are of vital importance. Although the pathophysiology of PCOS is not completely understood, abnormal hormonal responses arbitrated by ovarian granulosa cells (GCs) during the progression of follicular development are considered to be the primary cause [3]. Moreover, accumulating evidence has highlighted a strong correlation between PCOS, dysregulation of glucose homeostasis, lactate accumulation, and abnormal modulation of glycolytic enzymes in GCs, mainly due to augmented energy demands and increased Androgen receptor (AR)-mediated androgen actions during folliculogenesis [3–5]. In this context, the phosphoglycerate kinase 1 (PGK1), which catalyzes the conversion of 1,3-diphosphoglycerate into 3-phosphoglycerate, is known to be one of the most important ATP-generating enzymes in the glycolytic pathway [6]. Unfortunately, the specific mechanism by which it regulates glucose metabolism in GCs, which in turn leads to insulin resistance and other PCOS-related metabolic disorders is unclear.

In a recent issue of *EBioMedicine*, Liu and colleagues provided insight into this intricate molecular signaling by showing that PGK1 and AR play an essential role in the onset of ovulation disorders. Specifically, they identified PGK1 as a novel binding partner of AR in human GCs collected from patients who had undergone *in vitro* fertilization, revealing that PGK1 was more abundant in PCOS-luteinized GCs [7]. This PGK1-AR linkage was confirmed by an *in vivo* study in which mice with dehydroepiandrosterone (DHEA)-induced PCOS were treated with paclitaxel (PTX), a common chemotherapeutic drug used to combat ovarian cancers, which inhibits mitotic spindle disassembly [8]. Immunohistochemical and western blotting analyses revealed that PTX treatment reduced both AR and PGK1 protein expression levels in the ovarian tissue of PCOS-like mice, thus suggesting that PGK1 is related to ovulatory obstacles via AR signaling. In addition, co-immunoprecipitation assays performed in human HEK293T cells transfected with Flag-PGK1 and HA-AR, confirmed that PGK1 can bind to the AR. PGK-1 also regulated cell glucose metabolism in KGN cells, a human ovarian granulosa-like tumour cell line. Data from the same study showed that PGK1 inhibited AR ubiquitination levels, which enhanced AR stability via an E3 ligase SKP2-dependent pathway. As a result, PGK1 stimulated AR nuclear translocation, thereby regulating GC metabolism and the expression of several ovulation genes, which are the main actors of cell proliferation and apoptosis in PCOS pathology.

These findings suggest that the PGK1-AR axis represents an interesting avenue for exploring novel treatment targets to regulate the ovulation dysfunction associated with PCOS. Although the recent study by Lui and colleagues has thrown much-needed light on this intricate molecular signaling, many fundamental questions remain unanswered, and future research is required to clarify the mechanisms that could be used as potential strategies in the treatment of PCOS and its related metabolic dysfunction.

Contributors

Literature search: T.V., M. R. and V.M.V.; Data collection: T.V., M.R. and V.M.V.; Data interpretation: T. V. and V.M.V.; Writing: T.V., M.R. and V.M.V.

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Declaration of Competing Interests

The authors declare no conflict of interest.

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