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Review

Reviewing the molecular mechanisms which increase endometrial cancer (EC) risk in women with polycystic ovarian syndrome (PCOS): Time for paradigm shift?

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HIGHLIGHTS

- The molecular mechanisms linking PCOS and endometrial cancer are inconclusive.
- Hyperinsulinaemia and hyperestrogenism herald to genes over-expression in the pathogenesis of both PCOS and endometrial cancer.
- A paradigm shift into '-omics' research would yield a better understanding of the linkage.

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ABSTRACT

Endometrial cancer (EC) is the commonest gynaecological cancer in North American and European women. Even though it has been shown that women with polycystic ovary syndrome (PCOS) have a three-fold increase in the risk of developing EC compared to women without PCOS, the precise molecular mechanisms which increase EC risk in women with PCOS remain unclear. Clinical strategies to prevent EC in PCOS are therefore not well researched and understood. Although raised estrogen levels, hyperinsulinaemia and, reduced apoptosis have been suggested as potential mechanisms, there is a lack of clarity about how these factors and other factors may interact to increase EC risk in PCOS. This article reviews the literature, on the potential molecular links between PCOS and EC but argues for a paradigm shift, to a systems biology-based approach in future research into the molecular links between PCOS and EC. The potential challenges of a systems biology-based approach are outlined but not considered insurmountable.

Contents

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Introduction

Endometrial cancer (EC) is a significant cause of morbidity and mortality affecting women in the western world. The incidence appears to be rising with rising obesity rates. It is the commonest gynaecological cancer in North American and European women with 3874 per 100,000 women dying from the disease in 2010 in Europe [1]. There were 8300 uterine cancer cases in the UK in 2010 [1]. The incidence rate has increased by around 50% since the early 1990s. World-wide, more than 288,000 women were diagnosed with uterine cancer in 2008 making it the fifth most common cancer in women [1]. Research into measures to reduce EC risk in high risk populations is therefore vital to prevent deaths and improve the quality of life of women who may be affected. The risk factors for EC include obesity, nulliparity, type-2 diabetes, polycystic ovary syndrome (PCOS) (which affects 5–18% of women in the United Kingdom), insulin resistance, tamoxifen use and, exposure to estrogen therapy [2]. In a recently published systematic review [3], women with PCOS were about three times more likely to develop EC compared with women without the condition which translated into a nine percent lifetime risk of EC in Caucasian women with PCOS compared with three percent in women without the condition. The precise molecular mechanisms which increase EC risk in women with PCOS are however unclear [4].

The key hypotheses advanced so far to explain the link between PCOS and EC include raised estrogen levels, hyperinsulinaemia and reduced apoptosis in women with PCOS. Transcription factors (Sterol Regulatory Element Binding Protein-1) regulating intracellular lipogenesis have also recently been linked with EC but this has not been investigated in PCOS before. This article reviews the literature on the potential molecular links between PCOS and EC, but argues for a paradigm shift in research thinking to enable a better understanding of the mechanisms at play. This paradigm shift is in the move from a hypothesis driven approach to a systems biology-based one by leveraging the potential of new molecular biology and bioinformatics techniques that allow the study of several genes, proteins or molecules in one single experiment (genomics, proteomics and metabolomics) and the identification of new pathways and networks, to provide a better understanding of the links between PCOS and EC using computational biology. The potential challenges of the application of these techniques to the improved understanding of the mechanisms linking PCOS and EC are also outlined but not considered insurmountable.

Hyperestrogenism and hyperinsulinaemia

Previous attempts to explain the link between PCOS and EC have focused on the interplay between hyperestrogenism and hyperinsulinaemia. Unopposed estrogen as found in chronic anovulatory women with PCOS promotes endometrial growth and, proliferation. This acts by genetic and epigenetic mechanisms on cancer cells and has a strong influence on growth factors and oncogenes [5]. The epigenetic mechanisms include Epimutation and DNA hypermethylation [6]. Some specific changes associated with EC include changes in the expression of the hMLH1 gene and silencing of genes such as APC and CHFR, Sprouty 2, RASSF1A, GPR54, CDH1, and RSK4 by DNA hypermethylation [7]. Genetic mechanisms arising from DNA mismatch repair (MMR) have been correlated with the degree of aggressiveness of EC and the degree of expression of estrogen and progesterone receptor. For example in a study [8] of 70 EC biopsies from women aged under 40 years old, tumours with MMR protein loss were of higher grade, associated with worse clinical outcomes and showed lower estrogen receptor/progesterone receptor expression compared with tumours with retained staining for MMR proteins. With regards to insulin, insulin insensitivity resulting from reduced receptor binding and decreased insulin receptor mediated transduction leads to hyperinsulinaemia. In the liver, hyperinsulinaemia inhibits production of Sex Hormone Binding Globulin resulting in reduced production of Insulin Growth Factor Binding Protein (IGFBP). This causes exaggerated bioactivity of Insulin Growth Factors (IGF) 1/11. Both IGF1/11 promote ovarian steroidogenesis, enhancing androgen production in theca cells. This indirectly disturbs the ovarian–pituitary axis and intraovarian cycle [9]. Hyperinsulinaemia also activates cytochrome P450c17 alpha resulting in increased biosynthesis of ovarian and adrenal androgens [9]. Ultimately, androgen undergoes aromatisation to form estrogen. This cascade of endocrine and, steroid hormone metabolism acts synergistic and it is difficult to discriminate the exact insult which leads to EC in PCOS but it has comparable pathogenesis to that involved in the development of type-1 EC. Type-1 EC, is the more common of the two types of EC and accounts for approximately 80% of all types of EC. The well differentiated, endometroid adenocarcinoma (a subtype of type-1 EC) is associated with hyper-estrogenic states. It is however clear that hyperestrogenism is not solely responsible for the pathogenesis of EC in PCOS as there is some evidence that the links between hyperinsulinaemia and EC appear to be independent of hyperestrogenism. Diabetes mellitus which is associated with hypersinulinaemia for example, is linked with EC even in women receiving exogenous estrogens [10]. Diets, which improve insulin resistance such as a low glycaemic, index diet are also thought to reduce EC risk [11]. Higher insulin levels also have been found in postmenopausal women with EC [12]. In an in-vitro study evaluating the specific binding and growth promoting effect of insulin in EC cells culture, cancer cells derived from an adenocarcinoma that was negative for estrogen receptors had the highest concentration of insulin receptors [13] suggesting that the link between hyperinsulinaemia is linked with EC independent of estrogen. Cells derived from an adenosquamous carcinoma that was positive for estrogen receptors have also been found to have the least number of insulin receptors [14] suggesting that hyperinsulinaemia is an independent risk factor for EC in women with PCOS.

The exact molecular mechanisms linking hyperinsulinaemia as found in PCOS and EC are uncertain. It is however thought that it may be modulated by a direct effect of insulin and IGF on endometrial cells or alterations in the P13K-PTEN-AKT signalling pathway [15]. Both insulin and IGF receptors have been identified in both normal and malignant endometrium [16], and have been shown to have a mitogenic effect on endometrial cells in-vitro. IGF type-I receptor mRNA is over-expressed in EC [17]. The number of IGF type-I receptors have also been shown to positively correlate with the histological grade of EC [17,18]. Finally, insulin and insulin-like growth factor have been shown to accelerate the growth of EC cells in-vitro and it is thought that the mitogenic effect of high levels of insulin may be mediated through activation of the mitogen activated protein kinase pathway [19], increased expression of vascular endothelial growth factor [20] or by inhibiting apoptosis [12]. The PI3K-PTEN-AKT signalling pathway has been linked with regulating and promoting cell growth in type-1 EC and PI3K pathway alterations constituted approximately 80% of somatic alterations in EC [15]. The key modulation of this pathway is initiated by an increased IGF-1 and hyperinsulinaemia, which is pertinent in PCOS. Endometrial expression of genes associated with the IGF pathway and the P13K-AKT pathway has however not