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Pespective

PCOS and obesity: insulin resistance might be a common etiology for the development of type I endometrial carcinoma

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Abstract: Endometrial cancer (EC) is the most common gynecological malignancy in women and is the leading cause of cancer-related deaths worldwide. Estrogenic stimulation significantly increases endometrial cell proliferation, and both insulin resistance and hyperinsulinemia are associated with the development of EC in women. It has long been known that insulin resistance occurs in women with polycystic ovary syndrome (PCOS) and/or obesity, but one important unanswered question is whether the insulin resistance associated with PCOS and obesity is part of the etiology of the initiation and development of EC. Therefore, research efforts to understand the common and specific underlying endometrial responses to insulin resistance in women with PCOS and obesity could provide further therapeutic options for early endometrial carcinoma.

Keywords: PCOS, obesity, insulin resistance, estrogen, IGF-1, endometrial carcinoma

Introduction

Endometrial cancer (EC) is the most common gynecological malignancy in women and is the leading cause of cancer-related deaths worldwide [1]. In the US, there were 43,470 new diagnoses of EC and 7,950 women died from this disease in 2010 [2]. It has also recently been reported that more than 1,900 women die each year in the United Kingdom due to EC (http://www.cancerresearchuk.org). Approximately 25% of women with EC are pre-menopausal and 5% of all cases are diagnosed at less than 40 years of age [3]. Although numerous risk factors, including reproductive factors and obesity, have been implicated in the development of EC [4], the exact underlying molecular and cellular mechanisms involved in endometrial carcinogenesis and progression are not completely understood. Surgical procedures are still the first line and most effective treatments for the early stage of endometrial cancer [5], but such procedures preclude any further fertility. The significant individual and public health concerns associated with EC underscore the importance of understanding its etiologies as a means of prevention and for the development of effective nonsurgical treatments [6]. In this article, we provide an overview of current knowledge regarding the connection between estrogen production and the onset of EC. Because the common pathological complication between PCOS and diabetes is insulin resistance, we discuss how the interaction between PCOS, obesity, and insulin resistance can contribute to EC development.

Estrogens and EC

ECs can be classified as estrogen-dependent, well-differentiated type I endometrial-like carcinomas or as the less common, but clinically aggressive, estrogen-independent type II Fallopian tube-like carcinomas [4]. It have been estimated that 75%-85% of ECs are type I EC [5]. The development, progression, and metastasis of type I EC are strongly influenced by hormonal factors, and recent epidemiological stud-

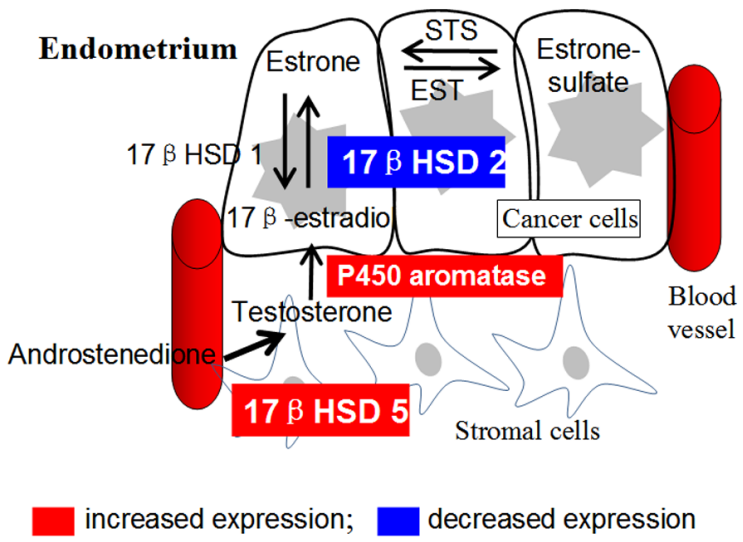

Figure 1. Local estrogen production in endometrial carcinoma. 17βHSD, 17β-hydroxysteroid dehydrogenases; EST, estrone sulfotransferase; STS, steroid sulfatase.

ies suggest that estrogen-driven proliferation might also be involved in the development of type II EC [7].

The endometrium lines the uterus and responds to cyclical steroid hormonal stimulation during the menstrual cycle [8], and EC originates in the single layer of epithelial cells that line the endometrium and form the endometrial glands [9]. It has been presumed that the primary cause of EC is the continuous exposure of the endometrium to estrogens [10, 11] that act as proliferative factors in the endometrial tissue and can lead to endometrial overgrowth and hyperplasia [9].

Hyperestrogenism can be exogenous or endogenous in origin, and a number of studies have shown that women with EC have aberrant alteration of local estrogen biosynthesis (**Figure 1**). For example, women with EC tend to have decreased expression of endometrial 17β-hydroxysteroid dehydrogenase (17βHSD) 2 and elevated levels of cytochrome P450 aromatase and 17βHSD 5 compared to healthy women [12]. Thus, the changes in steroidogenic enzymes might play a role in the elevated local estrogen levels seen in women with EC [13, 14]. In addition, endometrial estrogen production in cancer cells might amplify the effect of estrogens naturally produced in the ovaries and delivered via the circulation.

Polycystic ovary syndrome and EC

Polycystic ovary syndrome (PCOS) is the most common reproductive endocrine disorder in the world and affects approximately 4%-18% of all reproductive-aged women [15]. PCOS has adverse impacts on female endocrine activity, metabolism, and reproduction [16, 17] and is generally associated with chronic anovulation that results in a persistent progesterone deficiency. Thus, the endometrium in women with PCOS tends to remain in a proliferative state due to the lack of counterbalance by progesterone [11, 18]. Young women with PCOS have a high risk of developing EC [19], and it has been reported that PCOS women with endometrial hyperplasia have a four times greater risk of developing EC than non-PCOS women [20]. Although women with PCOS have an increased risk of developing EC [11], the risk is not the same in all women as evidenced by the fact that not all women with PCOS develop EC and not all women with EC suffer from PCOS.

Progesterone has been implicated as a protective factor against estrogen-driven growth and proliferation in the endometrium [1]. Progesterone-based oral contraceptives are used to inhibit endometrial hyper-proliferation and improve menstrual dysfunction [21], but approximately 30% of women with PCOS fail to respond to such treatment [22]. This results in the development and progression of atypical hyperplasia and further transformation to EC. Moreover, more than 30% of women with type I EC fail to respond to progesterone treatment due to progesterone resistance [23]. It is speculated that the persistence of an incomplete proliferative-to-secretory transition in the endometrium might result in progesterone resistance. This raises the question of whether progesterone resistance in women with PCOS might be a primary cause of EC. This seems unlikely to be the case, however, because progesterone resistance is also seen in women with endometriosis [22, 24] but is not associated with an increased risk of EC in these

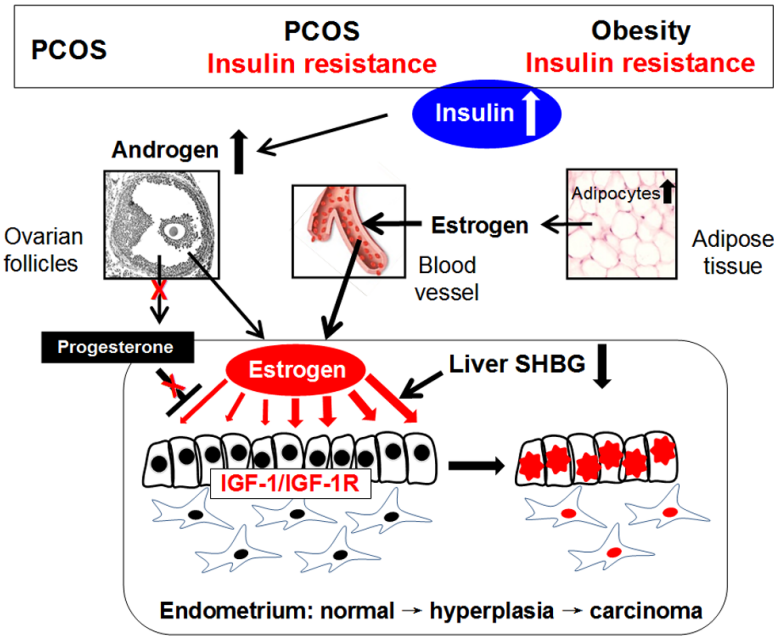

Figure 2. Clinical observations explained by the endocrine interactions linking insulin resistance and endometrial carcinoma development in women with PCOS and/or obesity. When insulin resistance occurs, both PCOS and obesity induce estrogen biosynthesis to activate estrogen receptor signaling in the endometrium. Activation of IGF-1/IGF-1R in epithelial cells further enhances the development of endometrial carcinoma. IGF-1, insulin-like growth factor-1; IGF-1R, insulin-like growth factor-1 receptor; SHBG, sex hormone binding globulin; ↑, increase; ↓, decrease.

women [25]. Thus, it appears that other as yet unidentified effects are involved in the development of EC in women with PCOS independently of progesterone resistance.

Of note, obesity is a common feature of PCOS [16, 17], and obese women with PCOS have a more abnormal endocrine and metabolic profile than lean women with this disease [26]. It has been reported that 50%-70% of women with PCOS exhibit insulin resistance [27], and this implies that an alternative pathological process might contribute to the development of EC in women with this disorder.

Obesity and EC

A variety of clinical and epidemiological investigations suggest that obesity and type 2 diabetes are strong risk factors for increased EC incidence and mortality [28]. Furthermore, a prospective study by Crosbie and colleagues [29] has shown a tight association between women with obesity (body mass index (BMI) > 30) or diabetic overweight (BMI > 25) and the onset of type I EC. Obesity develops through hypertrophy (enlarged adipocytes), hyperplasia (an increased number of adipocytes), or a combination of the two [30]. Adipose tissue is highly dynamic and insulin is a key hormone that regulates adipocyte volume and number [30]. Adipocyte dysfunction is a major contributory factor to obesity-related insulin resistance [31].

It has been demonstrated that estrogens can be produced by stromal cells in the adipose tissue in women [32]. In addition, because the preadipocyte cells in adipose tissues contain high levels of P450 aromatase, increased fat mass in women with obesity or diabetic overweight can enhance the aromatization of adrenal androgens and consequently increase the levels of systemic estrogens [33]. The levels of sex hormone binding globulin are decreased in obese women [33], and this can also contribute to increased activity of free estrogens that amplifies estrogenic activity in the endometrium (**Figure 2**). These hormonal changes might act in an additive manner to promote the development of EC in PCOS women with insulin resistance. Histological observations suggest that the enhanced endometrial proliferation in obesity is closely correlated to increased risk of type I EC [34, 35], and obesity and overweight are clearly associated with insulin resistance and hyperinsulinemia [36]. Thus, it is likely that the increased risk of EC in obese women is related to disturbances in steroid hormone regulation during the insulin-resistant state.

Insulin resistance and EC

Insulin resistance is traditionally defined as a decreased sensitivity or responsiveness to the metabolic actions of insulin. This results in a requirement for increased levels of insulin to achieve a given level of metabolic activity [37].

PCOS and obesity are linked through their common symptom of insulin resistance [27, 36].

Circulating insulin, acting in an endocrine fashion, is produced and secreted from β-cells in the pancreas and plays an essential role in glucose homeostasis by regulating the balance between hepatic glucose production and glucose uptake by adipose tissue and muscle [38]. Insulin has a variety of effects in different tissues and cells [39], and one explanation for insulin's ability to perform an array of biological actions in different tissues could be the differential expression and regulation of the two insulin receptor (IR) subunits IRα and IRβ [39]. The α-subunit contains the ligand-binding domain, and the β-subunit is activated by ligand-mediated autophosphorylation [39]. It has been shown that elevated levels of circulating insulin increase the aggressiveness of EC [40, 41] and are high risk factors for the estrogen-independent development of EC [41]. In humans, the expression of total IR and IRα is increased in endometrial carcinomas compared to normal endometria [42], and overexpression of IRα enhances the growth of EC cells in vitro [42]. These results suggest that activation of insulin signaling is directly involved in the development of EC in vivo. There is now an extensive body of evidence demonstrating the direct action of insulin in insulin-sensitive tissues including liver, muscle, and adipose tissues [39]. However, whether the mitogenic action of insulin plays a direct role in the carcinogenesis of the endometrium or whether insulin promotes carcinogenesis through its metabolic effects remains to be elucidated in the future [43].

The transition from normal to malignant endometrial epithelial cells involves changes in several different molecular pathways regulating normal cell proliferation and differentiation such as insulin-like growth factor-1 (IGF-1) signaling [44] (**Figure 2**). An elevated circulating IGF-1 level is an established risk factor for different types of human cancers [38]. Interestingly, IGF-1 null mice have hypoplastic uteri [45] and mice that overexpress IGF binding protein-1 (IGFBP-1), a negative regulator of IGF-1 signaling, have reduced IGF-1 responses in the uterus [46]. These results indicate the importance of the coordinated expression of IGF-1 and IGFBP-1 in normal uterine function. In the endometrium, estrogen increases the level of IGF-1 expression [47] but progesterone increases IGFBP-1 synthesis, which in turn inhibits IGF-1 expression and activity [33]. Moreover, insulin is also capable of increasing the bioactivity of IGF-1 through downregulation of IGFBP-1 synthesis in the endometrium [47]. Chronic hyperinsulinemia induces ovarian hyperandrogenism and increases peripheral aromatization of androgens to estrogen [47]. Thus, it is possible that normal endometrial cells undergoing this regulatory program described above might transform into EC cells as has been shown to occur with insulin resistance.

Sequence analysis has demonstrated that insulin and IGF-1 share 40%-50% homology and IRα and IGF-1 receptor share 84% homology [36]. Moreover, IR and IGF-1 receptor can assemble to form hybrid heterotetramers in response to both insulin and IGF-1 stimulation in an equivalent manner in vivo [48]. Because both insulin and IGF-1 can stimulate cell proliferation, it is possible that when endometrial cells co-express both IR and IGF-1 receptor the insulin and IGF-1 signaling pathways might cross talk with each other to contribute to EC development. Although insulin and IGF-1 activity appears to play an important role in the development of EC, several intercellular molecules, such as PI3K, PTEN, AKT, and mTOR, have been shown to play an important role in endometrial cancer cells [28, 43]. Given the impact of PCOS and obesity on insulin resistance and hyperinsulinemia (a surrogate marker for insulin resistance), we reason that PCOS and obesity share a common etiologic process, insulin resistance, for the initiation and development of EC.

Towards clinical management of early EC in women with PCOS

Clinical lines of evidence converge to support a stage-wise progression of endometrial hyperplasia associated with EC [4]. These stages include simple hyperplasia, complex hyperplasia without atypia, and complex hyperplasia with atypia [9]. Approximately 30% of PCOS women with atypical endometrial hyperplasia develop cancer if not treated [49]. Recent progress has been made in the treatment of women with PCOS and insulin resistance through a combinatorial strategy [37]. Our laboratory and others have shown that the combination of

metformin (*N,N*-dimethylbiguanide) and oral contraceptives are sufficient to reverse atypical endometrial hyperplasia in women with PCOS and insulin resistance, [50, 51]. Very recently, we have reported that similar treatment is capable of reverting early EC to normal endometria in addition to reducing insulin resistance in women with PCOS (Li *et al.* in submission). Metformin is a biguanide antihyperglycemic agent frequently used to treat women with type 2 diabetes. The most commonly described function of metformin is the reduction of insulin resistance and modulation of glucose metabolism in women with PCOS [52]. Our patients had insulin resistance with compensatory hyperinsulinemia before treatment. Thus metformin might have stimulated insulin activity in the endometrium in addition to other insulin-target tissues such as liver, muscle, and adipose tissues [39]. It is also possible that metformin might exert direct anti-tumor effects in the endometrium in vivo.

The initiation and development of EC is a complex and dynamic pathological process that involves a multitude of cellular pathways and signaling cascades [4]. The reversion from hyperplasia and/or carcinoma to normal endometria in response to combined treatment with metformin and oral contraceptives in women with PCOS is of great interest in both clinical medicine and basic research. Because type I EC occurs in young women with PCOS and insulin resistance, it will be interesting for future studies to investigate the cellular and molecular mechanisms of insulin resistance-induced type I EC in women with PCOS as well as to determine which processes do not lead to EC.

Conclusion and unresolved questions

Estrogen-dependent type I EC is the most common type of EC and is a socioeconomic and public health concern due to the potential for severe reproductive and gynecological consequences in women. Although it remains unclear exactly which autocrine and/or paracrine effectors lead to the initiation of EC, it is clear that an imbalance of steroid hormones significantly impacts endometrial pathology. A multitude of clinical studies have shown that both PCOS and obesity are associated with the development of type I EC. Due to significant variations in symptomatology in women with PCOS, and because most women already have established disease at the time of clinical presentation, the initiation and progression of EC in these patients has not yet been substantially explored. In addition, there are insufficient data to assess whether obese women with early type I EC tend to also suffer from PCOS and whether PCOS women who might develop EC require changes in insulin levels or endometrial insulin sensitivity. PCOS and obesity have insulin resistance as a common trait, and this raises the possibility that the two diseases might have similar ways of regulating insulin signaling in the endometrium. In addition, the insulin resistance found in both diseases might also contribute to dysregulated metabolism that drives EC development. Future studies are warranted to delineate the mechanistic connection between PCOS and obesity in women with insulin resistance during the development of EC.

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Disclosure of conflict of interest

The authors have nothing to disclose.

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