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Review article

Luteinizing hormone is a primary culprit in the endometrial carcinoma development in elderly women

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ABSTRACT

Endometrial carcinomas (ECs) are the most common gynecologic malignancies, exceeding the incidence of ovarian and cervical cancers in elderly women (post-menopausal) in Western countries. Evidence suggests that it is a luteinizing hormone (LH) dependent disease. ECs overexpress LH/human chorionic gonadotropin (hCG) receptors as compared with pre and post-menopausal endometria. Activation of the LH/hCG receptors in primary and immortalized EC cells results in an increased cell proliferation and invasion, which are mediated by cyclic AMP(cAMP)/protein kinase A (PKA) signaling, require the presence of LH/hCG receptors, activation of β_1 integrin receptors and an increase in the secretion of metalloproteinase-2 (MMP-2) in its active form. In addition to the endometrium, LH actions in the ovaries and adrenal glands results in an increased secretion of androgens, which are aromatized into estrogens in the adipose and EC tissues. LH also has direct effects in the pancreas, which results in an increase in insulin secretion, which in turn can also stimulate ovarian stromal cell proliferation, luteinization, androgens secretion and aromatization in adipose and EC tissues. LH is further elevated in post-menopausal women who develop EC as compared with post-menopausal women who do not develop the disease. These findings support complex network of LH actions that promote EC development in elderly women.

1. Introduction

ECs are the most common gynecologic malignancies with a higher incidence than ovarian and cervical cancers in Western countries.[1–3] Greater than 95% of endometrial carcinomas are adenocarcinomas.[1–3] The incidence increases with age, thus, 80% of ECs are seen among post-menopausal women.[1–3] Caucasian women are at a greater risk than black, Hispanic, Asian and Pacific Islanders, but black women are most likely to die from the disease.[4,5] The incidence of EC is on the rise without an increase in survival rates during the last four decades.[4–6] According to some estimates, there were about 55,000 new cases and 10,000 died from EC in 2015.[4,5] The estimated economic impact of this malignancy is about $2.6 billion per year.[6]

EC is a story of two diseases.[7,8] While type 1 disease is diagnosed in pre-menopausal women, type 2 disease primarily occurs among post-menopausal women.[7,8] The tumors from Type 1 disease are of endometriod histology, usually stages 1 or 2 and have a favorable prognosis. The tumors from type 2 diseases, on the other hand, have non-endometrial histology, including serous, clear cell, mucinous and other high-grade tumors. Type 1 disease is not usually aggressive, well differentiated, estrogen dependent, contain estrogen, and progesterone receptors (ER and PR), slow to spread and can be successfully treated with surgery or with progestins.[7,8] Type 2 disease, on the other hand, is aggressive, poorly differentiated, estrogen independent, do not contain ER or PR, vascular, spreads outside the uterus and has a poor prognosis that requires aggressive treatment.[7,8] Type 2 ECs show aneuploidy, p^{53} mutations, alterations in several genes, including those involved in cell cycle progression.[9–15]

Age, obesity, diabetes, reproductive and family history are some of the risk factors for type 2 EC development.[4,5,16–20] The risk is modulated by the degree of obesity, thus body mass index has a strong association with an increased risk.[4,5,16–20]

Type 2 ECs are associated with bleeding and also pelvic pain and pressure.[4,5] Definitive diagnosis is made by endometrial biopsy or may be suspected by transvaginal ultrasound and then confirmed by biopsy.[4,5] ECs are surgically staged tumors.[21] The early stages (stages I/II) are usually curable with an excellent 5 year survival rates.[21] Stage IV disease, on the other hand, has less than 10% survival rates at 5 years.[21] Based on the scientific data, we suggest that LH is a culprit in the type 2 EC development in elderly women.

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It works through a complex network of actions in several organs including the EC as well as ovaries, adrenals, adipose tissue and pancreas.

2. Evidence linking LH to EC

Several earlier studies have suggested that LH might be involved in the development of EC in post-menopausal women, based on the findings that circulatory LH levels were further elevated in women who developed EC as compared to those that do not develop the disease.[22–25] This suggestion has been validated by a study which demonstrated that ECs overexpress LH/human chorionic gonadotropin (hCG) receptors as compared with pre- and post-menopausal endometria.[26] This study also demonstrated that the receptor overexpression increased with the stage of the disease.[26] Subsequent studies have confirmed the receptor presence not only in ECs, but also in primary and immortalized EC cells.[27–35] The receptor expression was higher in carcinomas than in the surrounding microscopically normal endometrium and closely linked to aggressive tumor behavior.[30] LH was found to be mitogenic as well as to enhance invasion in primary and immortalized EC cells.[29,31,33] The EC cells that have higher LH/hCG receptor levels, showed a greater invasive potential when exposed to exogenous recombinant LH.[33] These actions are cAMP/PKA mediated and require the presence of the LH receptors.[31] The invasion, which is a prerequisite for metastasis, is promoted by an activation of β_1 integrin receptors, with a subsequent increase in metalloproteinase (MMP-2) secretion in its active form.[31] The mitogenic, invasion enhancing potential and other effects of LH/hCG have previously been demonstrated in normal cells.[36–63] These normal processes may have been amplified in EC, which is a hallmark feature of all carcinomas.

Circulatory LH appears to drive EC pathogenesis in elderly women. These levels (total/bioactive) are elevated up to seven fold in the women who have developed EC than the cohorts who do not develop EC.[22,64] Therefore, LH seems to be an important factor. But it alone may not be sufficient, as most elderly women with elevated LH levels do not develop the disease. Therefore, genetic or epigenetic and other inherent risk factors may also be required.

3. LH actions in EC

LH has several effects in the normal human endometrium that are relevant to implantation of blastocyst and its limited invasion into endometrium and pregnancy continuation.[39,42–44,46,49–52,54–62,65,66] When some of the normal actions are dysregulated, the potential exists for LH to initiate malignant changes that might lead to the development of EC. The LH actions in normal endometrial cells fall into proliferation, invasion, angiogenesis, and apoptosis categories.[39,42–44,46,49–52,54–62,65,66] Even though, the latter two have not been demonstrated in the context of EC development, there is a reason to believe that they may occur. For example, type 2 ECs are highly vascular and the increased vascularity could come from the LH, which is a vasoactive hormone in its own right. For example, uterine vasculature contains LH/hCG receptors and their activation results in the formation of new blood vessels as well as dilation of the existing ones.[54,67–71]

4. LH actions in ovaries, adrenals, adipose tissue, and pancreas may contribute to the EC development

The mechanism of LH action to induce EC may also involve its actions in the ovaries, adrenals, adipose tissue, and pancreas, through functional LH/hCG receptors in these tissues.[72–78]

The ovaries of post-menopausal women actively secrete androgens from the stromal cell compartment and LH can stimulate this secretion.[79–95] The ovaries of women with EC are even more active in androgens secretion than cohorts without EC.[85,89,92–94,96] The increased secretion comes from hyperplasia and luteinization of stromal cells and greater elevation of LH levels.[22,63,64,96–99]

The role of the adrenal glands in EC development is related to an increase in LH levels, which can stimulate zona fasciculate to secrete androgens. In fact, (a) age associated increase in LH levels correlate with an increased adrenal function in post-menopausal women,[100–103] (b) hCG challenge increases adrenal androgens secretion in older female macaques[104] and finally (c) hCG can stimulate androgens secretion from human adrenal cortical cells.[75]

Adipose tissue involvement in EC pathogenesis is related to an increased aromatization of androgens from adrenals and ovaries, which is perhaps under LH and/or insulin control. However, there is no evidence yet for the LH control, but this may not be a far-fetched possibility, considering that it contributes to the aromatase regulation in ovaries. Insulin, on the other hand, seems to be able to regulate aromatase in fat tissue.[105] Activation of LH/hCG receptors has been shown to increase cell proliferation, differentiation, and leptin secretion from preadipocytes.[76] These actions are mediated by cAMP/PKA independent mitogen activated protein kinase yet (MAPK)/c-fos signaling.[76] Whether or how these LH actions could contribute to EC pathogenesis is not known.

The involvement of the pancreas in EC development in post-menopausal women is related to the hyperinsulinemia, a known risk factor in type 2 ECs.[4,5,106] In fact, EC patients often have elevated insulin levels and an increased insulin resistance.[106] The higher insulin levels could come from LH stimulation of β-cells of pancreas.[77] However, it is not known whether LH can also contribute to increased insulin resistance. Nevertheless, the increased insulin levels can stimulate ovarian stromal cells proliferation, luteinization, secretion of androgens, and their aromatization in EC tissue.[106–111]

Post-menopausal women regardless of EC have elevated androgen levels.[84,92–95,100–102] These elevated levels come from a secretion from adrenals as well as ovaries, both of which are stimulated by LH.[72,103,104] The androgens are then converted to estrogens in adipose and endometrial tissues.[111–114] This conversion is increased in post-menopausal women who develop EC, as compared to those who do not develop the disease.[109,112] These increases likely come from LH and insulin stimulation because their levels are elevated during EC pathogenesis[64,106] and the tissues themselves contain their receptors.[64,105–107,110,115,116] In fact, insulin can regulate aromatase in endometrial and adipose tissues.[105,111] Whether LH is also involved is not known. But it is not a far-fetched possibility. Estrogens formed from androgens result in only a small increase in circulation, perhaps due to differences in metabolic clearance rates, conversions to other steroids and the level and binding capacity of sex steroid binding globulin (SHBG).[92]

The increased aromatization in EC tissue and potential further stimulation by LH and/or insulin could result in a high local estrogen concentration in the tumor microenvironment. The role of these estrogens is not known, but they are not likely to induce type 2 EC because the tumors do not contain ER.[1–3] What roles do these estrogens play, remains to be investigated.

Fig. 1 presents the proposed model on how LH can induce type 2 EC in elderly women. Future research will undoubtedly bring several modifications to this model.

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