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Review

The role of sex hormones and steroid receptors on female reproductive cancers

Luiz Gustavo de Almeida Chuffa [a,*], Luiz Antonio Lupi-Júnior [a], Aline Balandis Costa [b], João Paulo de Arruda Amorim [c], Fábio Rodrigues Ferreira Seiva [d]

[a] Department of Anatomy, IBB/UNESP, Institute of Biosciences of Botucatu, Univ. Estadual Paulista, SP, Brazil
[b] Department of Nursing, UENP/CLM – Universidade Estadual do Norte do Paraná, PR, Brazil
[c] Department of Anatomy, UNIOESTE/FB – Universidade Estadual do Oeste do Paraná, PR, Brazil
[d] Department of Biology and Technology, UENP/CLM – Universidade Estadual do Norte do Paraná, PR, Brazil

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ABSTRACT

Sex steroids have been widely described to be associated with a number of human diseases, including hormone-dependent tumors. Several studies have been concerned about the factors regulating the availability of sex steroids and its importance in the pathophysiological aspects of the reproductive cancers in women. In premenopausal women, large fluctuations in the concentration of circulating estradiol (E2) and progesterone (P4) orchestrate many events across the menstrual cycle. After menopause, the levels of circulating E2 and P4 decline but remain at high concentration in the peripheral tissues. Notably, there is a strong relationship between circulating sex hormones and female reproductive cancers (e.g. ovarian, breast, and endometrial cancers). These hormones activate a number of specific signaling pathways after binding either to estrogen receptors (ERs), especially ERα, ERα36, and ERβ or progesterone receptors (PRs). Importantly, the course of the disease will depend on particular transactivation pathway. Identifying ER- or PR-positive tumors will benefit patients in terms of proper endocrine therapy. Based on hormonal responsiveness, effective prevention methods for ovarian, breast, and endometrial cancers represent a special opportunity for women at risk of malignancies. Hormone replacement therapy (HRT) might significantly increase the risk of these cancer types, and endocrine treatments targeting ER signaling may be helpful against E2-dependent tumors. This review will present the role of sex steroids and their receptors associated with the risk of developing female reproductive cancers, with emphasis on E2 levels in pre and postmenopausal women. In addition, new therapeutic strategies for improving the survival rate outcomes in women will be addressed.

Contents

* Corresponding author at: Department of Anatomy, Institute of Biosciences of Botucatu, UNESP – Univ. Estadual Paulista, Zip Code: 510; P.O. Box: 18618-970, Rubião Júnior, s/n, Botucatu, SP, Brazil.
E-mail address: chuffa@ibb.unesp.br (Luiz Gustavo de Almeida Chuffa).

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1. Introduction

1.1. General overview of sex steroids and their receptors

Estradiol (E2) and other sex steroid hormones circulate in the bloodstream specially bound to sex hormone-binding globulin (SHBG), a well-described glycoprotein synthesized by the liver [1,2]. The bioavailability of E2 to target cells is strictly related to SHBG. Sex steroids and their receptors have a profound involvement in diverse human diseases, including hormone-dependent tumors [3,4]. Estrogens promote physiological actions after binding to their estrogen receptors (ERs) subtypes (ERα and ERβ). These receptors belong to the family of ligand-activated nuclear receptors. ERα is highly expressed in bone, reproductive organs, kidney, liver, and white adipose tissue, whereas ERβ is expressed in the prostate, ovary, bladder, uterus, and the central nervous system [5]. ERs share important domains with other members of the family, and N-terminal A/B domain is a specific region that confers direct actions on target genes. Notably, this region is responsible for the activation function-1 (AF-1) that is ligand independent, and promotes distinct cellular activities. The central C-domain is highly conserved in both ERα and ERβ, and presents a DNA binding domain, which leads to receptor dimerization. The C-terminal E-domain represents the ligand binding domain (LBD) that contains AF-2 region, and ERα and ERβ display a 59% conservation [6]. ERs act as dimers to regulate gene transactivation, and this event is mediated by a synergic function between AF-1 and AF-2. Unlike ERα, ERβ seems to have a weaker AF-1 function and is more dependent on the ligand for transactivation [7]. ERs can be activated by numerous ligands including ER activators such as tamoxifen and raloxifene, ERβ agonist diarylpropionitrile, ERα agonist propylpyrazole-triol, and other molecules [8]. Importantly, the estrogen response occurs after binding of ER to estrogen-responsive elements (EREs) followed by nuclear activation complex for the transcription of target genes. Estrogen can also exert their effects via non-genomic signaling through cell membrane ERs, which are regulated by downstream signaling molecules such as mitogen-activated protein kinase (MAPK), and protein kinases A and C [6].

The progesterone (P4) actions are dependent on progesterone receptor (PR), a member of the family of nuclear hormone receptor [9]. Essentially, PR is described with two isoforms, being the N-terminal-truncated A (PRA) and the full length B (PRB) [10]. In general reproduction, the progesterone responses are related to PRA in females, and conversely, PRB is essential for regulating normal proliferative responses [11]. P4 binding to PR elicits a structural change resulting in segregation of heat shock proteins, followed by dimerization, and binding to specific DNA promoter sites as P4 response elements. This process requires the participation of proper co-activators leading to transcriptional activation or repression [12].

Testosterone (T) acts through classical and non-classical signaling [13]. Although the well-known nuclear/cytosolic androgen receptor (AR), which works as a ligand-activated molecule, the involvement of AR in the non-genomic pathway remains controversial [13]. While a number of studies showed the main role of the nuclear/cytosolic AR in both classical and non-classical signaling pathways [14,15], others evidenced a membrane-bound receptor from the GPCR family, as mediator of T-induced effects in different tissues and tumor cells [16–18].

1.2. Sex steroids in pre and postmenopausal women

In premenopausal women, E2 is largely produced by the granulosa cells of the ovarian follicle, and aromatase CYP450 enzyme is responsible for the conversion of T and androstenedione into E2 and estrone, respectively. The production of E2 is cyclical and regulated by feedback control to follicle-stimulating hormone (FSH), with fluctuations in the concentrations of E2 and P4 throughout the menstrual cycle during follicle development [19]. The expression of aromatase is common in peripheral tissues such as skin and adipose tissue, where activity is modulated by other signals including c-AMP, prostaglandins, and glucocorticoid [20]. After menopause, E2 and P4 output from ovaries decline, but the production of circulating E2 remains in the peripheral tissues. The concentration of E2 is not subject to large fluctuations in postmenopausal women [21], being fairly constant and low (10–60 pmol/l) in comparison to those observed in younger women (70–1500 pmol/l).

T is produced by the ovary, adrenal gland, and through peripheral conversion of androstenedione. Despite T decrease with aging, their levels do not appear to be severely affected by menopause [22]. In the early 1940s, T was reported to restore libido and ameliorates menopausal symptoms [23]. Recently, evidences have emerged on the hypothesis that the decline in T levels is linked to a decrease in libido, quality of life, and worse moods [24], and further exogenous androgens replacement associated with E2 can improve the symptoms affecting sexual function and related disorders [25].

Despite conflicting results, most postmenopausal women presenting high levels of hormones including E2, T, and estrone are at potential risk of developing ovarian, breast, and endometrial cancers (Fig. 1). Regarding tumor microenvironment, we also need to consider that external sources of estrogen and aromatase can drastically affect prognosis, especially in obese patients. In this line, adipose tissue inflammation associated with the recruitment of immune cells (e.g. macrophages) can favor the local production of estrogens in breast tissues, and it is possible that these effects may also be recognized in tumor-associated macrophages (TAMs) related to high expression of aromatase [26–28].

1.3. Ovarian cancer

1.3.1. Different histotypes and the role of sex steroids

Ovarian cancer (OC) is the second most common and lethal gynecologic malignancy. Due to its advanced stage at the moment of diagnosis, OC presents with the highest mortality rate. About 90% of these subtypes are epithelial ovarian cancer (EOC), and unfortunately, 70% are late diagnosed with widespread metastasis [29]. Therefore, new therapeutic strategies and reliable screening