Androgens and ovarian cancers

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Summary

Ovarian cancer is one of the most lethal malignancies in women. Numerous studies indicate that the steroid hormones have been implicated in the etiology and/or progression of epithelial ovarian cancer and support a role for androgens, including: 1) androgen receptor (AR) is present in primate ovaries at almost all stages of the menstrual cycle and involve folliculogenesis and ovulation; 2) high androgen serum levels show high risk of ovarian cancer and ovarian cancer occurring after menopause when the balance of ovarian steroid production shifts from estrogens to androgens; 3) ovarian cancer tissue shows a 90% AR positive rate and is associated with favorable outcomes; 4) androgens promote or inhibit ovarian cancer cell growth; 5) chemotherapy decreases androgen production from cancer cells. This review seeks to summarize our current understanding about the roles of androgens, AR and AR coregulators in the initiation and/or progression of ovarian cancers.

Key words: Androgen; Androgen receptor; Androgen receptor co-regulators; Anti-androgen; Anti-oxidant; Ovarian cancer.

Ovarian cancer is one of the most lethal malignancies in women, the fifth leading cause of cancer-related deaths in North American women [1], and the tenth leading cause of cancer-related deaths in Taiwan [2]. Its incidence has been increasing recently in Asian countries such as China, Singapore, and Taiwan [2-7]. Greater than 90% of ovarian cancers are common epithelial cancers [5].

In the last two decades, much progress in the treatment of ovarian cancer has been reported [5, 6]. In 1975, when Griffiths related the duration of survival to the diameter of the largest residual cancer [8, 9], and several studies have since confirmed this [6, 10-12]. Of most importance, advanced surgical technique, anesthesia support, and intensive postoperative care significantly decrease the residual burden of the residual cancer. However, surgery alone can not treat diseases successfully even after aggressive surgical intervention is performed partly because of the presence of some residual tumor and partly because of high recurrence of tumors; therefore, adjuvant postoperative chemotherapy is nearly always needed to attempt to gain complete clinical remission [13, 14]. In fact, ovarian cancer was one of the first solid tumors treated with cytotoxic drugs with a chance of successful control although the duration might be short [15, 16].

In the last 20 years, despite the introduction of diverse and powerful chemotherapeutic agents, the survival rate for epithelial ovarian cancer has changed little [17-27]. Two-thirds of patients present with advanced stage disease for which few effective treatments are available, and more than 50% of the patients die from the disease within five years of diagnosis. So far, there is no rationale showing any benefit for a long-term administration of adjuvant chemotherapy or other unspecified therapies. Therefore, using a potential "reagent" similar to dietary antioxidants or steroid analogues that are the option of chemoprevention for cancer [29], provides us with a good alternative for maintaining the remission status in patients with ovarian cancers. Among these, the analogues of curcumin, estrogens (tamoxifen), androgens, retinoid acids, vitamin D, and vitamin E possess the potentiality. In fact, the function of many nuclear receptors including androgen receptor (AR) is modified during treatment with one of the above-mentioned analogues [29].

Androgens and androgen receptor in normal ovaries

Androgens are produced primarily in the form of testosterone (T) by theca cells in the ovary and are generally found circulating throughout the body [30], although the circulating level of T is relatively low in women [31-35]. In fact, when women are found to have high serum levels of T, an underlying androgen-secreting tumor will be first considered, especially from ovarian stromal cells, for example, steroid cell tumors, theca cell

tumors, and Leydig cell tumors [31-35]. In addition to the ovarian androgens, adrenal androgens, such as androstendione, dehydroepiandrosterone (DHEA), and its sulfate, are secreted by the adrenal cortex. Although not as potent as T, adrenal androgens do contribute to the androgenic effects in the body.

Androgens are a major hormonal product of the ovary, both pre- and postmenopausally. Production of androgen in the theca cells is regulated through the hypothalamic-pituitary-gonadal axis [36-38]. The hypothalamus secretes pulses of gonadotropin-releasing hormone (GnRH) every 90-120 minutes. GnRH binds to gonadotropes in the anterior pituitary and stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). When LH reaches the theca cells, it stimulates production of androgen, which serves as obligatory substrates for estrogen synthesis, subsequently, transporting into the granulosa cells to produce a large amount of estrogen, which feeds back on the pituitary to inhibit the secretion of GnRH and FSH. Androgen effects are often mediated through the AR. AR is present in primate ovaries, including human and other mammalian ovaries, at almost all stages of the reproductive cycle. Exogenous androgens influence *in vivo* follicular development either for promotion or for inhibition. In addition, greater amounts of AR protein in the granulosa cells of small antral follicles compared with larger antral follicles have been observed in pigs, rats, and primates, and greater amounts of AR might facilitate FSH actions in early antral follicles, a critical period of FSH influence on follicular development, by positively regulating FSH receptor.

Androgen and androgen receptor

As previously indicated, androgen effects are often mediated through AR. AR, a phosphoprotein, functions as an androgen-dependent transcriptional regulator [39-41]. AR is composed of four major domains: an N-terminal transcriptional activation domain AF-1 (A/B domain), a central DNA-binding domain (DBD) (C), a hinge region (D domain), and a C-terminal ligand-binding domain (LBD), which contains a second activation function, AF-2 [42]. AR is found in many tissues of both sexes but is most abundant in male reproductive tissues and the female ovary. The best characterized functions of AR are to promote the growth and differentiation of the male urogenital structures [30]. AR knockout ($AR^{-/-}$) male mice show severe abnormality of prostate development and penile growth, and are infertile [43]. In contrast, it is very interesting to find that AR is not essential for developing female reproductive organs and fertility, although the efficiency of reproductive function shows some degree of impairment [44]. AR is capable of being phosphorylated, and reversible phosphorylation appears to play a role in both ligand-dependent and ligand-independent AR activation [30]. Before binding its ligand, AR is thought to be in an inactive state, in which it is bound to at least two heat-shock proteins (hsp90 and hsp70) and other cellular chaperones [30, 42, 45-48]. In this state, AR is inactive and unable to influence the transcription rate of its target gene promoters [49, 50]. Once T has entered the cell, it is usually converted to DHT by 5α-reductase or serves as a substrate for synthesis of estrogen in ovarian granulosa cells. AR is capable of binding to both T and DHT. In fact, DHT has a higher affinity for the AR (approximately 2- to 10-fold). Upon binding with the androgen or ligands, AR undergoes a series of events, including conformational changes, dissociation from heat shock protein complexes, dimerization, phosphorylation, and nuclear translocation. The activated AR is able to recognize palindromic DNA sequences, called androgen response elements (AREs), and form a complex with AR-associated proteins to induce the expression of AR target genes [51]. The binding of hormones to the AREs causes the recruitment of co-activators and basal transcription machinery, leading to the upregulation of target gene transcription.

Androgen receptor and androgen receptor co-regulators

AR co-regulators include co-activators and co-repressors, which are both required for efficient modulation of target gene transcription by steroid hormone [42]. AR co-activators are factors that can interact with AR in a ligand-dependent manner and enhance gene transcriptional activity. AR co-repressors are factors that interact with AR, either in the absence of hormones or in the presence of anti-hormones, and repress gene transcriptional activity. Therefore, changes in the expression level and pattern of steroid receptor co-activators or co-repressors, or mutations of their functional domains can affect the transcriptional activity of the steroid hormones and hence cause disorders of their target tissues [42]. Several AR co-regulators [52, 53], including

androgen receptor-associated proteins (ARAs) such as ARA 54 [54, 55], ARA55 [56, 57], and ARA70 [21, 58-61], cyclic adenosine monophosphate (cAMP) response element-binding protein (CBP) [62], p160 co-activator [63], and tumor suppressor genes, such as retinoblastoma (Rb) [64] and BRCA1 [21, 65, 66] have been evaluated. It has been proposed that co-regulators function as a bridge between activators and the basal transcription machinery [67-70], through the modification of nucleosomal structures or the efficient recruitment of basal transcription machinery [69-70]. Results from these studies suggest that co-regulators not only enhance AR transactivation, but may also be able to increase the agonist activity of anti-androgens and 17-β estradiol (E2) in prostate cancer cell DU145 cells [71]. However, the role of co-regulators for AR transactivation in ovarian cancer cell lines has not been clarified so far although one report found that ARA70 expression is activated in invasive ovarian cancer tumor cells, and amplification of androgen action by ARA70 may be involved in the etiology/progression of this disease [21, 72].

BRCA1 is a breast cancer susceptibility gene, and its inherited mutations are correlated with an increased risk of breast and ovarian cancers [4]. BRCA1 was shown to co-activate p53 and modulate p300/CBP expression, and function as a ligand-independent co-repressor for estrogen receptor (ER), progesterone receptor (PR) and AR [42]. In contrast, BRCA1 was shown to enhance the ligand-dependent AR transactivation in both breast and prostate cancer cell lines, especially in the presence of exogenous steroid receptor co-activator (SRC) family [66]. These contrasting results of BRCA1 influence on AR activity are somewhat controversial. ER and PR play key roles in breast cancer development and progression, and AR signaling in the breast has a protective effect [42]. Thus, it is reasonable to speculate that the normal expression of BRCA1 probably protects the breast from tumorigenesis by suppressing the ER and PR signaling pathway and promoting AR activity. Therefore, mutations of the BRCA1 gene increase the risk of developing cancer [42]. Our limited data from studies of the transactivation of BRCA1 on AR in ovarian cancer cell lines also showed relatively inconsistent results, which pointed out the more complicated roles of BRCA1 in the development of ovarian cancers. Other co-regulators are the SRC family including SRC-1 (nuclear coactivator 1: NcoA-1), SRC-2 (TIF2/GRIP1/NcoA-2), and SRC (p/CIP/RAC3/ACTR/AIB1/TRAM-1), steroid receptor RNA activator (SRA), protein inhibitor of activated signal transducer and activator of transcription (PIAS1, and PIAS3), small nuclear ring finger protein (SNURF), and so on [42].

Evidence of the role of androgen in ovarian cancer

Steroid hormones have been implicated in the etiology and/or progression of epithelial ovarian cancer [73, 74], although their roles are not fully understood. Among these steroid hormones, androgen may be important. First, ARs are present in primate, including human, ovaries at almost all stages of the menstrual cycle, and androgens mediated by AR may play an essential role in follicular growth and maturation, atresia, and luteinization as autocrine or paracrine agents since continual ovulation is a possible explanation for ovarian carcinogenesis [73-75]. Second, more than 90% of ovarian cancer tumors express AR [76-79] and high AR expression has previously been shown to be associated with lower-stage ovarian tumors and better patient survival [80]. Third, a high level of androgen shows an increased risk of ovarian cancers either in clinical or animal studies [81-83] and the incidence of ovarian cancer is highest after menopause, when androgens are the main steroids produced by the ovary [33]. Fourth, androgen production increases in ovarian carcinomas and decreases during response to chemotherapy [84]. Fifth, androgens can modify the growth of ovarian cancer cell lines although the data are not always consistent [74, 85-89]. Sixth, since the CAG repeat present in the N-terminal region of the AR inversely correlates with AR transactivation activity, Santarosa *et al.* found that the AR-CAG repeat length could play a role as modifier of the ovarian cancer risk conferred by high penetrance genes rather than itself conferring a low risk [90]. However, Spurdle *et al.* did not find any evidence to support the correlation between AR-CAG repeat and risk of ovarian cancer [91]. Seventh, Edmondson *et al.* found that the ovarian surface epithelium is an androgen responsive tissue and that androgens can cause an increase in proliferation and a decrease in cell death, so they suggested that androgens have important implications in the pathophysiology of ovarian carcinogenesis [92]. Although these results are somehow inconsistent, they provide a rationale to study the real relationship between androgens and ovarian cancers.

The potential role of anti-oxidants in treating ovarian cancer via the androgen receptor pathway

Vitamin D_3 (1, 25-dihydroxyvitamin D3 [1, 25(OH) $_2D_3$]) and androgens are essential for the regulation of growth and differentiation in a variety of target organs [93]. The receptor proteins for vitamin D3 (VDR), just like AR, belong to the superfamily of nuclear receptors. Vitamin D_3 exerts a variety of physiological effects, such as inhibiting growth and inducing differentiation in normal and malignant cells, including prostate, ovarian, endometrial, mammary, and other cancer cell lines [93-97]. The presence of VDR has been demonstrated in human ovarian tumors by ligand-binding assay [93] and in rat ovaries by immuno-histochemistry [98]. Furthermore, epidemiological studies have indicated that UV radiation, the major source of the vitamin D_3, precursor vitamin D, may constitute a protective factor against ovarian cancer [99]. Although the roles of vitamin D_3 and VDR in ovarian growth and differentiation have been reported [87], their mechanisms and correlations with androgens or AR have not been defined. In addition, vitamin E, a commonly used anti-oxidant, was reported to have effects on anti-tumor growth [100]. So far, its mechanism has also been unclear although one result indicates that vitamin E could effectively down-regulate the protein level of AR, which could be one of the major reasons accounting for vitamin E-mediated growth inhibition in prostate cancer cells [101]. Using anti-oxidants against tumors is still a highly interesting and controversial field, and most importantly, it presents a very exciting and impressive topic in the thought process of chemoprevention for cancer.

Conclusion

Much evidence supports the importance of androgens in initiation and/or progression of ovarian cancers. The understanding of the mechanisms of action of the androgens on ovarian cancers will be helpful for the development of new cancer therapies.

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