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ROLE OF ESTROGEN IN TREATMENT OF PROSTATE CANCER

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ABSTRACT

Prostate development and disease are androgen and estrogen dependent. However, the nature of hormonal effects on the prostate of healthy young men is not clear. Although the mechanism underlying the hormonal induction of prostate cancer remain uncertain. Estrogens have already been reported to stimulate proliferation of cultured prostate cancer cells, primarily through receptor-mediated effects. Estrogen therapy plays a role in the management of castration-resistant prostate cancer. Although the mechanism of action is not fully known. This current analysis reports the relationship of change in adrenal androgen levels and prostate-specific antigen response in patients with CRPC treated with estrogen therapy. Estrogen not only associated as ER-mediated effects, even by other activities like DNA, genetically etc. Antiestrogen can be best therapeutic agents for the prostate cancer prevention.

KEY-WORDS: Prostate Cancer, Estrogen, Estrogen Receptor

INTRODUCTION

Prostate cancer is the most common non-skin cancer in men (1). Human prostate cancer is generally known as androgen dependent while estrogen is also important in both the normal as well as malignant prostate. Locally produced or metabolically transformed estrogens may differently affect proliferative activity of prostate cancer cells. Prostate development and disease are androgen and estrogen dependent. However, the nature of hormonal effects on the prostate of healthy young men is not clear (2). In maintenance of structure and integrity of prostate androgens and estrogens plays important role after sexual maturity (3, 4), If we see the past of prostate cancer treatment, we will find that estrogens was primary treatment for the metastatic prostate cancer for many years but have been superceded in the past two decades by luteinizing hormone-releasing hormone (LHRH) agonists, primarily because of the cardiovascular toxicity associated with oral estrogen therapy (5-8).

Estrogens in combination with androgens appear to be required for the malignant transformation of prostate epithelial cells. Although the mechanism underlying the hormonal induction of prostate cancer remain uncertain. Estrogen has already been reported to stimulate proliferation of cultured prostate cancer cells, primarily through receptor-mediated effects. The importance of estrogen effects on the mature human prostate has been known for decades, although these effects are complex (9, 10). Jin and colleagues in 1996 (2), present study demonstrates that in genetic male transsexuals, chronic administration of high dose estrogens reduces total prostate volume.

Estrogen therapy plays a role in the management of castration-resistant prostate cancer (CRPC), although the mechanism of action is not fully known. This current analysis reports the relationship of change in adrenal androgen levels and prostate-specific antigen (PSA) response in patients with CRPC treated with estrogen therapy (11).

ESTROGEN RECEPTORS

There are two main receptors of the estrogens: i). ERα, ii). ERβ. Both receptors are expressed in both normal and diseased human prostate. Both the receptors different functions eg. ligand binding, heterodimerization, transactivation, and estrogen response element activity. Their expression imbalance may change the estrogen effects on prostate cancer cells. ERβ activation is directly linked with cell proliferation or to ERα inhibition and on other hand loss of the ERβ consistently associated with tumor progression in prostate cancer. Only little amount of data is available regarding the expression and function of the Estrogen receptors in the human prostate (11).

With scenario regarding the estrogen receptor, ERβ has challenged for the reevaluation of the estrogen role in the prostate carcinogenesis, with expression of ERβ more than ERα in normal prostate epithelium and again loss of the expression of the ERβ emphasizes on possible role in development of cancer (5).

PROSTATE CANCER & ESTROGENS

Evidences showed that plays an important role in predisposing or causing the prostate cancer (12-19). Elevated plasma estrogens are responsible for the risk of prostate cancer (20, 21). Some studies also mentioned just opposite finding, as

increasing prostate cancer risk associated with decreasing estradiol levels after adjusting for sex hormone-binding globulin (22), while some meta-analyses could not mention any link about increasing level of estrogen and risk of prostate cancer (23-25). When we talk about the prostate cancer risk in animal models, especially in rat, estrogen required condition for the prostate carcinogenesis, although rats do not naturally develop prostate cancer, it can be induced by combined treatment with estradiol and testosterone (26-28).

ESTROGEN METABOLISM

Estrogen plays important role from menstrual cycle and reproduction to modulation of bone density, brain function, cholesterol mobilization etc. (29-31). It has been clear from numerous studies association of estrogen with development and progression of several kinds of cancers mainly breast, endometrium, ovary, prostate, lung, and colon (31, 32). Estrogen is a classical etiological factor for prostate cancer. In this review, we focus on the estrogen mechanisms in prostate carcinogenesis with discussion on current anti-estrogen strategies in prostate cancer treatment.

MOLECULAR MECHANISMS

With respect to molecular mechanism of estrogen in prostate carcinogenesis, estrogen mediates its biological effects in prostate tissues by binding to specific intracellular receptors, estrogen receptor ER-α and ER-β (33). There are many studies to describe the complex molecular mechanisms of estrogen-ER action. This complex based on the ligand – protein comples formation and activated transcription factor to regulate expression of genes (34-36). ERα and ERβ are encoded by *ESR1* and *ESR2*, respectively. These receptors ERα and ERβ are widely expressed in tissues of prostate. ERα and ERβ are highly homologous in their DNA-binding domains and possess moderate sequence identity in their ligand-binding domains. Only they are different by the hormone-independent transcriptional activation function (37).

SIGNALING

Estrogen signaling in prostate cancer can be understood by the mechanism of carcinogenesis. With genetic marker mechanism of prostate cancer related with oncogenic effects of estrogens (38) with some newer treatments against prostate cancer based on regulating paracrine signaling within the tissue itself. It essential component of androgenic control of prostate cancer gland (39, 40). Being uncertain results of clinical trials against the prostate cancer yet also it is clear that estrogen signaling in prostate very complex by presence of only two receptors. These receptors appear to play significantly different roles in the prostate, with ERα mediating the adverse and ERβ mediating the beneficial effects of estrogen (40).

PHYTOESTROGENS

In contrast with the use of plant products natural estrogens and dietary estrogen analogs has been proposed against the prostate cancer development as well as treatment. This can draw the interest of researchers towards the phyto-products as anti-cancer, mainly phytoestrogen for example one of the phytoestrogen from soy isoflavones as genistein (41).

GENOTOXIC ACTIVITY

In the growing body of evidence to suggest that estrogens might act as carcinogenic factors not only through the ER but also through a genotoxic mechanism (42). Some indications regarding site of cancer development have the lower no. of enzymes that protect against catecholestrogens and redox-cycling (43).

As conclusion we can say and give evidence from animal studies that estrogens can have genotoxic activity in the rat prostate and that this might be related to induction of cancer by estradiol plus testosterone. There are at present no human data in this regard.

ABLATION THERAPY

On the basis of observations in pre-clinical studies, estrogen ablation therapy has been proposed for prostate cancer treatment, mostly with cells in culture. *Selective ER modulators* (SERMs) as antiestrogens, are also used as ablation therapy.

CHEMOPREVENTION

It is a mechanism of inhibition of development of premalignant lesions or of their progression to cancer by pharmaceutical agents or nutriceutical compounds. For prostate it is widely used for already existing cancer (44). So as an important factors chemoprevention agents have multiple anti-cancer activities. For examples possibly SERMs might have multiple activity against prostate cancer. This might provide them with a broader spectrum of chemopreventive activity than pure antiestrogenic agents. At the same time, it is critical that SERMs used as chemopreventive agents are very safe and have no genotoxic or other adverse properties.

CONCLUSION

With conclusive remark we can directly link the Estrogens and ERs development and progression of prostate cancer. Estrogen not only associated as ER-mediated effects, even by other activities like DNA, genetically etc. And antiestrogen can be best therapeutic agents for the prostate cancer prevention.

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