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ROLE OF SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERM) IN TREATMENT OF CARCINOMA PROSTATE.

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ABSTRACT

The exact mechanism of carcinogenesis is unknown, although it is believed to involve a combination of dietary, environmental, genetic, lifestyle and hormonal causes. Prostate cancer is main problem of men, and it is believed that prostate cancer is the hormonal imbalance of the testosterone but now it has been proved clinically that estrogen hormone imbalance is also involved in the prostate carcinogenesis during the development or later period of the prostate. It required maintaining the balance of the estrogen hormone by some estrogen receptor. In this review we focused on the literature survey on Selective estrogen receptor modulators (SERMs) in prostate carcinogenesis and prevention because SERMs have shown the ability to prevent and treat prostate cancer.

KEYWORDS:- Prostate Cancer, SERM, Estrogen, Estrogen Receptor

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INTRODUCTION

Prostate cancer is main problem of men. Despite all the significant efforts of researchers, scientists, oncologists, doctors etc., the exact mechanism of carcinogenesis is unknown, although it is believed to involve a combination of dietary, environmental, genetic, lifestyle and hormonal causes. Huggins first demonstrated the androgenic dependence of prostate cancer as a potential cause, as well as a point of intervention and therapy, ultimately leading to a Nobel Prize in 1966 (1, 2). Now it has proved experimentally that with the imbalance of the estrogen during the prostate development or later can lead to progression of premalignant lesions to prostate cancer. By same experimentally it also has proved that these developments can be inhibited by the inhibition of the estrogen, while there may be lot of side effects due to estrogen regulatory mechanisms in prostate along with other hormonal effectors (3).

CHEMOTHERAPEUTIC STRATEGIES

Chemotherapeutic strategies against prostate cancer may be of great impact both medically as well as economically (4). The basis of chemoprevention is the ability to interfere with prostate carcinogenesis, and as a consequence, prevent prostate cancer with drugs. Previously researchers focused their work on the androgen hormone for the prostate cancer, but recently estrogens have been used as potential agents in the development and progression of prostate cancer (5). Estrogenic stimulation through estrogen receptor α in a milieu of decreasing androgens contributes significantly to the genesis of benign prostatic hyperplasia, prostate dysplasia, and prostate cancer (6). Prostate carcinogenesis suppression by anti-estrogens and selective estrogen receptor modulators (SERMs) is supported by preclinical, clinical, and epidemiological studies (4).

ESTROGEN RECEPTORS PRESENCE IN PROSTATE

Stroma and epithelium of prostate contains estrogen receptors. Both animal models and human epidemiologic studies have implicated estrogens as an initiator of prostate cancer. In the aging male, prostate cancer occurs in an environment of rising estrogen and decreasing androgen levels. Selective estrogen receptor modulators (SERMs) have shown the ability to prevent and treat prostate cancer, suggesting that they may be used in prostate cancer chemoprevention (7).

ROLE OF ESTROGENS

Prostate development and function is regulated by the estrogens by means of direct or indirect mechanism. Primarily growth, differentiation and function of the prostate are controlled by androgens but by several different ways these are modulated by the estrogens. The most important routes of indirect estrogen regulation are interference of androgen production by repression of the hypothalamic–pituitary – gonadal axis and direct effects on the testis. Another important, indirect route for estrogen regulation of prostate is via prolactin. Estrogens also clearly have direct effects on prostate, which may be elicited by external hormone or by estradiol produced by local aromatisation of testosterone. It has been very difficult, however, to work out the mechanisms and the physiological importance of these effects (3, 8,9). With reference to all the observations of the previous studies, it is clear that cancer risk and changes in prostate is due to estrogens, while still we are unable to draw exact mechanism of the prostate cancer. Proposed mechanisms include epigenetic modifications, direct genotoxicity, hyperprolactinemia, immunotoxic or inflammatory changes, and prostatic ER-mediated changes (5).

IMPORTANCE OF SERMs

SERMs are drugs that bind to the estrogen receptor (ER); in some tissues they act like estrogen (agonists), while in other tissues they oppose the action of estrogen (antagonists)

(10). The SERM acts as an estrogen antagonist to prevent and treat cancer, but it acts as an estrogen agonist in the endometrium, to induce cancer (10). SERM with attractive features for prostate cancer chemoprevention as favorable safety profile and efficacy in preclinical models (4, 11, 12). Primary hormonal functions of Estrogens are mediated by the estrogen-specific receptors. These receptors possibly showing the functions against the estrogens and are spread in all tissues with highly expressed in estrogen-sensitive tissues (13). The activation of the multiple ERs leads a number of phenotypic changes in prostate tissues. Direct estrogen signaling pathways within prostate cells play an important role in the development of the prostate gland and possibly in the development of cancer (14-19). ERα, ERβ and GPR30 are three proteins have tissue-dependent distribution and different effects on cell phenotype and activity (20-22). As discussed later, the activity of endogenous estrogens or dysregulation by exogenous estrogens on any or all of these receptors may play a role in prostate cancer development and/or progression.

MECHANISM-BASED DRUG DISCOVERY

With the present and coming modern technologies drug discovery can play important role in cancer prevention. The classic drug development is based on ligand receptor binding. While work is focused towards understanding the molecular determinants of ER pharmacology may lead to incorporation of functional assays as primary drug screens. This “mechanism- based” approach to drug discovery should, in theory, permit identification of novel classes of modulators.(23, 24) Three mechanism-based approaches to new SERM discovery that are currently being put into practice are described in brief below: Cofactoromics, ER subtype- selective modulators, and pathway- targeted SERMs (25).

MOLECULAR MECHANISMS OF ESTROGEN

Specific intracellular estrogen receptors (ERα and ERβ) binds to the estrogen in target tissues (26). By great effort of the researchers the complex molecular mechanisms of estrogen-ER action came in existence. This function of estrogen is ligand activated transcription factor to regulate the expression of multiple target genes (27-30).

FUTURE PROSPECTS

After review of results of the studies regarding prostate cancer, estrogen as well as SERM, the development of the new SERM can be a exciting results in the field of prostate cancer prevention as therapeutic potential. Further researches regarding different receptors, with specific functions may be the future pharmacologic treatment for the prostate cancer (31-44).

CONCLUSION

The term ‘selective estrogen receptor modulator’ has raised new hope that tissue-specific estrogens or anti-estrogens can be designed. To avoid the concerns about the use of traditional hormone replacement therapy, dehydroepiandrosterone—a tissue-targeted precursor of sex steroid formation—offers hope of a physiological tissue-targeted hormone replacement that, combined with a SERM, would simultaneously prevent breast and uterine cancer.

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