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PRODRUG AND RECEPTOR MEDIATED DRUG TARGETING STRATEGIES OF PROSTATE CANCER

NAVEEN G.* AND SEETHA DEVI A.

Department of Pharmaceutics, Hindu College of Pharmacy, Guntur.

ABSTRACT

Prostate cancer is the most leading cause for death in elder male patients after lung cancer. It was age dependent and was not easily identified through symptoms due to its slow advancement from local small prostate tumors to highly metastasized prostate cells located in local lymph nodes and bones and most of patients die with the disease without prior detection. Negligence or identification in late stage lead to evolution of anti androgen therapy resistant cancer indicating the need of targeting of drug to both localized prostate cancer cells and metastasized cells. Prodrugs and receptor targeting agents can help in targeting specifically cancerous prostate cells by taking advantage of biological process that occur in cancer cells. They are reliable targeting agents which make therapeutic agents to be available at site of action for maximum potentiation of action and there is a need for progressive research in this field.

KEYWORDS: **Prostate Cancer, Prostate specific antigen (PSA), Prodrug, Prostate-Specific Membrane Antigen (PSMA), Prostate Stem Cell Antigen (PSCA), Aptamer.**

*Corresponding author

NAVEEN G.
Department of Pharmaceutics, Hindu College of Pharmacy, Guntur.

INTRODUCTION

PROSTATE ANATOMY

Prostate is a chest nut sized exocrine gland with secretory function of male reproductive system, present below the urinary bladder surrounding beginning of urethra. It is enclosed by fibrous capsules and the tumor confined inside capsule until it is punctured. Gland is divided into lobules by urethra and ejaculatory ducts from testes. The excretory ducts from prostate lined by secretory cells, ejaculatory ducts join urethra at prostate gland. The secretory cells under influence of androgens renew replacing older cells and secrete fluid consisting of spermine, zinc, citratic acid, alkalisers which neutralises acidic conditions of vagina to keep sperm cells active, prostate specific antigen(PSA) with serine protease activity breaks clot formed by proteins produced by seminal vesicles before ejaculation. Prostaglandins and other proteolytic enzymes are also present which assist in fertilization. PSA acts as tumor marker and is major tool used in earlier detection of prostate cancer[1,2,3].

The prostate is divided into three parts[4]:

1. Peripheral zone: consists of about 70% of total gland and is major origin site of cancer
2. Transitional zone: present around the proximal urethra and consists of 5% of total gland and 10-20% of prostate cancers can occur in this area
3. Central zone: consists of 25% of total gland and 2.5% of prostate gland occur in this area

ROLE OF ANDROGENS IN PROSTATE CANCER

Prostate gland at the time of birth is in a size of small pea and gradually increases with the increase of age and attain normal size at the age of early twenties and the susceptibility of incidence of cancer increases with age especially from early forties. Androgens especially testosterone play a major role in growth and maintenance of prostate. The secretory epithelium under the influence of testosterone secreted by testes under influence of luteinizing hormone replicates and secretes prostatic fluid through androgen receptor(AR) mediated mechanism. Secretory epithelium consists of two types of cells- basal and secretory cells. The basal cells under influence of dihydro-testosterone(reduced form of testosterone by 5α reductase) differentiate into secretory cells whose secretory activity which in turn is under influence of AR bound dihydrotestosterone. Over expression of AR receptor or mutation in AR expressing gene or alteration of androgen signaling can cause uncontrolled division of secretory epithelium and stromal cells under influence of androgens leading to tumor formation. Androgen blocking strategies of using anti androgen, LHRH agonists, estrogens are effective in treating metastatic prostate cancer[5].

PRODRUG AND RECEPTOR MEDIATED TARGETING STRATEGIES

According to National Cancer Institute, Maryland there are identification of 238,590 new cases of prostate cancer and 29,720 death cases are reported in 2013. Treating of cancer depends on its stage and stage of cancer is measured by Gleason scale or TNM (tumor, node, metastasis) or Whitmore-Jewett staging by observing prostate tissue biopsy samples. This staging or grading of cancer determines the treatment. These grading systems categories the cancer from slow growing localized cancers to aggressive metastasized cancers. In case of slow growing prostate cancer the cancer localized within the capsule with the absence of metastasis and patient may die without identification of disease. If identified in this early localized conditions, tumor is treated by castration, prostatectomy or radiation. Highly metastasized cancer spread to bones, lymph nodes and far body parts and when identified in late stages it will become unresponsive to treatment and surgery. Metastasized cancer is treated with androgen ablation therapy which will become unresponsive due to genetic alteration in cancer cells after 12-18 months of initiation of treatment. In many cases early detection and treatment of prostate cancer did not proved the increase of life expectancy[6]. This indicate a need for development of new therapies and identification of different cellular process including at molecular levels which will become new targeting strategies for treating prostate cancer. The present review concentrate on receptor and prodrug targeting strategies which can be effective in treating

prostate cancer basing on molecular activity and physiology of prostate cancer cells.

PRODRUGS

Chemotherapeutic agents are best agent of choice for treating highly metastasized malignancies. Prodrug form of these agents increases therapeutic efficiency of anti-cancer agents by the release of cytotoxic agents by selective metabolism of target cells. Prodrugs include a carrier molecule linked with drug molecule which on metabolism in target site release the active drug. This strategy of prodrug is widely used in chemotherapy to reduce the toxicity and unwanted effects of chemotherapeutic agents. The main requirement of prodrug is its stability in blood, its metabolism in its specific target and unwanted side effects of carrier.

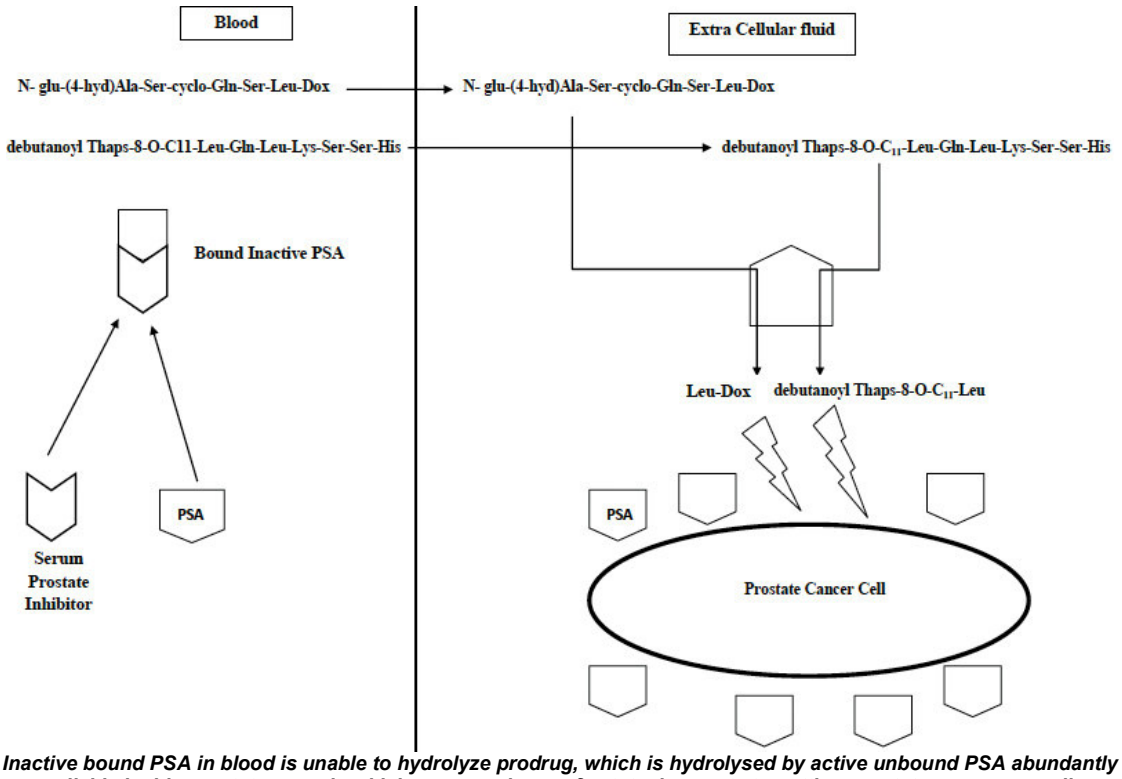
Prostate specific antigen (PSA) mediated targeting

PSA is a glycoprotein which belongs to human kallikrein family that exhibits serine protease activity with molecular weight 28,400 Da comprising 237 amino acid residues. It has effect of tumor invasion and metastasis by activating urokinase-type plasminogen activator[7] and also increases tumor growth by the release of active IFG-I by cleaving insulin-like growth factor binding protein 3 (IGFBP-3)[8]. PSA is synthesized in secretory epithelium of the prostate and passes into excretory ducts and mixed at the time of ejaculation with semen stored in the seminal vesicles to produce seminal liquefaction by its protease activity. Less amount of PSA is absorbed into the bloodstream where its levels are less than 4 ng/ml. The prostate capsule acts a barrier that prevents the escape of PSA into blood circulation. The disruption of this capsule by tumor allows more PSA into the circulation and these increased levels are used as diagnostic tool for prostate cancer. The concentration of PSA in the prostate extracellular fluid is 1600-2100 nM in normal human prostate and primary human prostate cancer which is enzymatically active. In contrast, PSA is found in the sera in enzymatically inactive form[9] due to its complexation with serum prostate inhibitor α_1-antichymotrypsin and in lesser instant with α_2-macroglobulin and other serum enzyme inhibitors[10,11]. Higher the malignancy, higher PSA production and extracellular concentration in prostate and lower serum PSA levels due to increase of bound PSA[12]. This fact is used for targeting cytotoxic agents to prostate cells by using carriers which can acts as substrates for PSA. Semenogelin I and II are the major gel-forming proteins in ejaculated semen on which PSA acts and slice them into fragments[13]. PSA cleavages semenogelin I between Gln349 and Ser350 in its chain[14,15]. This helped in preparation of short peptides hydrolyzable by PSA which can act as carriers, and peptide with sequence of His-Ser-Ser-Lys-Leu-Gln (HSSKLQ) is identified with high degree of specificity for PSA. This peptide is linked with C-terminal carboxyl group to the amino group of the drug doxorubicin (Dox) to yield a Dox-peptide conjugate. Invitro cell culture studies using human prostate cell line LNCaP revealed that PSA was unable to hydrolyze the amino bond between the Dox-amine and the C-terminal glutamine of the peptide. A slight modification of addition of L-leucine linked to amine group of doxorubicin and producing a prodrug yielding peptide with sequence of HSSKLQ-Leu-Dox prodrug, which is active and easily hydrolysable by PSA yielding cytotoxic agent Leu-Dox than its precursor peptide conjugate. Modification of this prodrug by protecting free amino acid end and cleavage site yields prodrug (N-glutaryl-(4-hydroxyprolyl)Ala-Ser-cyclohexaglycyl-Gln-Ser-Leu-Dox) that can be selectively and actively cleaved by PSA releasing Leu-Dox[16,17,18]. It lacks complete metabolism into Leu-Dox when administered to different laboratory animal models like mice, rats, dogs and monkeys and abundant production of Leu-Dox by non PSA metabolism fails this prodrug[19]. Thapsigargins are sesquiterpene lactones found in the genus *Thapsia* belonging to the family Apiaceae and in *Laser trilobum* (Apiaceae). These act as cytotoxic agents that can be conjugated with carrier peptide. They act by inhibiting SERCA (sarco/endoplasmic reticulum calcium ATPase) pump causing depletion of intracellular Ca^{2+} leading to sustained elevation in cytosolic Ca^{2+} concentration causing apoptosis of proliferating quiescent G_0 cells. For production of thapsigargin prodrug, thapsigargin is converted into *O*-8-debutanoylthapsigargin and esterified with the *O*-8 with amino acid

linkers like 12-(L-leuinoylamino) dodecanoyl and conjugated to the PSA hydrolysable peptide[20,21]. Moreover the cytotoxin produced from PSA hydrolysis is highly lipophilic and taken up membranes of cancer cells which is produced in their vicinity limiting uptake of neighboring cells[22].

Figure 1

Mechanism of action of prodrug Prostate specific antigen (PSA) mediated targeting



Inactive bound PSA in blood is unable to hydrolyze prodrug, which is hydrolysed by active unbound PSA abundantly available inside prostate capsule which causes release of cytotoxic agents targetting prostate cancerous cells.

Prostate-Specific Membrane Antigen (PSMA) mediated targeting

PSMA is a membrane bound glycoprotein with glutamate carboxypeptidase activity present in prostatic epithelium and over-expressed in malignant prostate tissues, especially in the hormone refractory disease. Through its carboxypeptidase activity it removes terminal γ-glutamate residues from poly-γ-glutamated folates and folic acid are transported into cell for utility of cell. This presence of over expressed PSMA in prostate epithelium is used for targeting pore forming peptides[23,24]. Amoebapore is a pore-forming toxin isolated from pathogenic *Entamoeba histolytica,* of 77 amino acid residues with molecular weight of 8244. Four α-helical domains are contained within the toxin. H-3 is 25 amino acid residues in length is part of amoebapore and highly capable of inserting itself into lipid bilayers with a pore-forming activity causing leakage of electrolytes and cellular contents leading to cellular death. It is modified by attaching two glutamate residues to the lysine end of H-3 toxin gives a peptide acting as prodrug with sequence Gly-Phe-Ile-Ala-Thr-Leu-Cys-Thr-Lys-Val-Leu-Asp-Phe-Gly-Ile-Asp-Lys-Leu-Ile-Gln-Leu-Ile-Glu-Aps-Lys-(γ-Glu-γ-Glu)-NH_2 used for targeting cancer cells. This modification make the toxin ineffective but gets activated at cells with high membrane bound PSMA concentration and specifically kills prostate cancer cells by PSMA hydrolysation of glutamate residue producing active pore forming H-3 toxin. But this strategy of targeting PSMA has a drawback of its presence in brain and salivary tissues limiting its usage[25,26].

Tomoregulin targeting

Tomoregulin is a transmembrane protein of unclear function in prostate cancer, selectively expressed in the brain, prostate, and prostate cancer cells act as antigen for antibody 2H8 which is a murine IgG1 monoclonal antibody that reacts with the follistatin domains of the

extracellular region of tomoregulin protein. Tomoregulin is highly expressed in luminar epithelial cell of secretory epithelium located in cancerous prostate, normal prostate and brain where the activity of 2H8 is limited by impervious blood brain barrier. 2H8 has higher affinity towards tomoregulin but its binding don't alter any cellular activity inhibiting tumor growth. this binding tendency is utilized for radioimmunotherapy. Radiotherapy is an effective approach for the treatment of both local prostate cancer and highly metastasized tumors locate in bones and lymph nodes. Hence 2H8 is a good carrier for radionuclides for targeting. Radionuclides like ^{111}In (Indinium-111), ^{90}Y (Yttrium-90) are conjugated with 2H8 lead these agents to accumulate in tumor leading death of cancer cells through radioactivity[27]. Besides radioimmunotherapy, tomoregulin conjugated toxins are found to be therapeutic option for treatment. Many plant toxins like ricin, saporin, bacterial toxins like diphtheria toxin are conjugated with antibodies for this purpose. 2H8-saporin conjugate after binding to tomoregulin is internalised into vesicle structures of cytoplasm by receptor-mediated endocytosis pathway releasing saporin by lysosomal proteolysis. Free saporin by RNA N-glycosidase and inhibits protein synthesis by cleaving one specific adenine base from ribosomal RNA and inducing irreversible ribosomal damage[28].

Prostate Stem Cell Antigen (PSCA) targeting

PSCA is a glycosylated glycosylphosphoinositol-linked cell surface antigen expressed in normal prostate, urinary bladder, kidney, and placenta. Its expression is found in primary and metastatic prostate cancer as well as in neoplasms of the urinary bladder, esophagus, and pancreas . In normal prostate its expression was highly present in secretory epithelial cells whereas its level of expression is higher in metastatic disease rather than localized non-malignant prostate disease[29]. Three monoclonal antibodies 6F8, 8D11, and 5F2 are identified by ELISA that reacts strongly with PSCA protein on the surface of live cells. These antibodies shows greater affinity towards PSCA and found to decrease the rate of tumor growth than normal untreated tumors by internalization of antibodies via the caveolae pathway of uptake. These PSCA specific antibodies shown better results when used as both in unconjugated and toxin conjugated forms. Toxin conjugates consists of antibody acting as leading carriers linked with toxins like calicheamicin and maytansinoid 1 (DM1) toxins which have shown efficacy with limited toxicity. Immunotoxin 8D11-DM1 conjugate shows better invivo results by rapid decrease in tumor volume with complete eradication of established tumors in the majority of animals and invitro activity on MCF7.Her2.gD.PSCA, PC3.gD.PSCA, PC3.neo cells. DM 1 acts by inhibiting the polymerization of tubulin into filaments and thus interferes with the formation of the mitotic spindle in mitotically active cells. It has low therapeutic index for clinical usage and cause potential side effects in case of epithelial cells with high cellular turn over. These side effects can be reduced by conjugating it with PSCA specific antibody 8D11 which carries or directs DM 1 to PSCA antigen expressed cell. At the site of targeting 8D11 binds to the PSCA antigen initiating internalization of DM 1 toxin through caveolae pathway releasing free DM 1 toxin intracellulary by peptidase activity of cell. The cells with lesser expression of PSCA antigens are shown to be less effected by conjugated antibody by in vitro cytotoxicity on the bladder cancer cell line SW780[30]. PSCA antibody can also be conjugated with radionuclides like ^{131}I (Iodine-131) for targeting prostate cancer cells[31].

Prostate-Specific Membrane Antigen (PSMA) targeting

J591 is an anti-PSMA deimmunised monoclonal antibody that binds with high affinity to the extracellular domain of PSMA. MLN2704 is an immunoconjugate designed by attaching J591 antibody with DM 1 toxin intended to deliver DM 1 toxin to PSAM expressing prostate cells act by the mechanism as mentioned in above section. It is found to be effective when administered intravenously every 4 weeks in patients with progressive castration-resistant disease, with mild toxicities[32]. Another approach of linking radionuclides like ^{90}Y , ^{111}In with J591 antibody direct these radioactive isotopes to the PSMA expressed cells leading to the death of cancerous cells due to radioactivity of

these isotopes[33]. Anti PSMA antibody-dendrimer conjugates usage is another strategy involving antibody is linked with dendrimers like PAMAM (Polyamidoamine) dendrimers for benefit of better aqueous solubility, biocompatibility and well as well to carry ligands like radionuclides for minimum loss of radioactivity[34].

Aptamers targeting Prostate Specific Membrane Antigen (PSMA)

Aptamers are RNA or DNA oligonucleotides that fold by intramolecular interaction into unique three-dimensional conformations capable of binding to target antigens with high affinity and specificity. Conjugated aptamers leads toxins like gelonin and radionuclides to PSMA expressed prostate cells. RNA aptamer (A9) with sequence 5'-GGGAGGACGAUGCGGACCGAAAAAGACC UGACUUCUAUACUAAGUCUACGUUCCCA GACGACUCGCCCGA was used as carrier to target gelonin which is a ribosomal toxin, a small N-glycosidase protein with a molecular weight of 28 kDa, causes cell death by cleaving a specific glycosidic bond in rRNA causing disruption of protein synthesis in PSMA prostate cancer cells[35].

CONCLUSION

The goal of development of complete regimen of prostate cancer treatment is not till achieved[36]. These prodrugs and receptor targeting agents remained promising agents for targeting chemotherapeutic agents whose systemic toxicity is reduced by narrowing its activity and concentrating their activity towards targets which are cancerous cells . Various carriers are used in targeting prostate cancer including prodrugs, antibodies, toxin and radionuclide conjugated antibodies, aptamers showing promising results in targeting different targets or receptors expressed on cancer cells. There is a need for identification of more antigens or target sites and design of carriers targeting prostate cancer.

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