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Review Article

Experimental Animal Models for Prostate Cancer - A Mini Review

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Abstract

Prostate cancer is a second leading disease among men worldwide. Epidemiological studies reveal American men highly prone to get, the occurrence of prostate cancer is increased in developing countries like India may to due to changes in the lifestyle, food habit. Prostate cancer is an age-related disease in men. Sex steroid hormones like testosterone play a significant role in the prostate cancer formation. For analyzing various molecular and cellular mechanism involved in prostate carcinogenesis, researchers using various models like transgenic mouse model, xenograft model, syngeneic models, chemically induced prostate cancer, etc. Literature indicates that there is constant endeavor by the researchers towards developing prostate cancer models that mimic carcinoma of the prostate in human. However, the all experimental animal models seem to have some advantage and disadvantage. Model creation for a prostate cancer is still a challenging phenomenon and a developing process. Thus data generated through animal model study in this branch seems to be intriguing confront in terms of model and therapeutic outcome for that may be model specific. This mini-review highlights the current scenario.

Keywords: Prostate cancer; Animal model; Transgenic; Xenograft; Syngeneic; Chemically induced prostate cancer

Introduction

Prostate cancer is the second most predominant cancer in men worldwide, especially in western countries. Age-related incidences of prostate cancer are men who have more than 50 years of age. Difficulty in urination, frequent urination, hematuria, poor streaming of urine is major signs and symptoms of prostate cancer. Even in benign condition also people suffered from poor urinary outflow. According to Global Health Observatory data- WHO, 2018 [1], incidences of prostate cancer were much higher in America regions includes North America, followed by Europe, New Zealand, Australia, etc. and its incidences were low in south East Asian countries. But this epidemiological works reporting that even, developing countries in Asia like India shows that increase in various cancer populations including prostate cancer in men.

In developing countries like India, the national cancer registry program reported based population-based registry across India, in that metropolitan city like Delhi, Pune, Kolkatta, Thiruvananthapuram, Bangalore, Mumbai, Chennai showing increasing in the incidence of prostate cancer. In that Chennai is the fourth leading city for prostate cancer incidence [2]. A noticeable report was supposed to consider, in USA migrants from Asian countries were highly susceptible to get incidence of prostate cancer rather previously. The reason for which is, changing of lifestyle, environmental factors and food habit etc [3]. A same Global Health Observatory data- WHO reporting high-income countries were showing ten times increasing of prostate cancer compared to middle and low-income countries. But least prevalence of certain cancer like prostate cancer also was increased in developing countries. It seems that preparation and analyses of epidemiological data regarding prostate cancer from time-to-time are highly recommended for a given population.

Recently, many researchers are focusing oncology area because as day by day incidence of various cancers increased irrespective of sex and age. Researchers were used the various model to work in various cancer to understand the biology of various cancer cells and develop therapeutic agents to treat such cancers. Likewise, for prostate cancer we are using various in-vivo and in-vitro models. This mini-review focused on prostate cancer and its models.

Materials and Methods

We have collected articles from various internet sources like Google scholar, Pub Med and so on. The collected articles were meticulously reviewed and thoroughly analyzed.

Prostate cancer

A review starts with a brief anatomico-physiological and histology of prostate gland. The prostate is a major accessory sex organ in men. The main function of it is contributing for semen. But in human beings prostate contains various zones rather individual like in laboratory animals. Mc Neal classification or division of zones of the human prostate was widely accepted until date. Human prostate consist of peripheral zone (high incidence of carcinoma, chronic prostatitis, and post inflammatory can occur), central zone, transition zone (high incidence of age-related Benign Prostatic Hyperplasia (BPH), low incidence of adenocarcinoma can occur) and anterior fibromuscular stroma was present [4]. But unlike human beings, laboratory animals like rat, mouse having different lobes rather zones. They are ventral lobe, dorsal lobe, and lateral lobe.

The histological architecture of human prostate contains two cell layers one is luminal secretory columnar epithelium and the other

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one is a basal layer. The lumen contains multi lamellated eosinophilic concretions called corpora amylacea. These features were commonly seen in aged subjects. Coming to rat prostatic histology, all three lobes contains tightly packed acini with stroma. Glandular acini consist of cuboidal epithelium [5,6]. But in rat, the dorsal and lateral lobes together called as a dorsolateral lobe. The rat dorsolateral and anterior prostate or coagulating glands are homologous to peripheral zone and central zone of the human prostate gland [7].

These dorsolateral lobes were very homologous to human prostate where a high incidence of cancer will occur. Though the dorsolateral lobe of mouse and the peripheral zone of the human prostate were homologous but according to Bar Harbor Pathology Panel dorsolateral lobe of mouse and the peripheral zone of the human prostate have no direct relationship [8], they are dissimilar anatomically [9].

Prostate cancer is mainly an adenocarcinoma because mainly it is developed from the glandular region. Cancer facts and figures of American Cancer Society (2016) [10], reports a characteristic clinical feature of prostate includes difficulty in voiding urine due to pain and burning, weak streaming of urinary flow, difficult in start and stop of urination, blood in the urine (hematuria) and frequent urination especially at night times. The above-mentioned signs and symptoms were observed at an advanced stage of prostate cancer, not in an early stage. American cancer society's prostate cancer data have stated that occurrence of prostate cancer might be due to aging, race (African Americans), geography (North America, northwestern Europe, Australia, etc), family history, diet (high-fat diet) and obesity. Prostate-Specific Antigen (PSA) level determined as a diagnostic for prostatic disease especially prostate cancer.

Endocrine system also plays an important role in some kind of cancers, especially prostate cancer. Testosterone is a male hormone responsible for maintenance of male phenotype after puberty. Its biological importance not only observed in adolescence but also during development i.e testosterone is most important for development growth and maintenance prostate gland [11]. In general, inside the prostate, testosterone is a more potent form called dihydrotestosterone (DHT) by an enzyme 5-alpha reductase. This enzyme is off in the form of two isoforms. They are type I and type II [12]. Prostate cancer is off two different kinds 1) androgen dependent and 2) androgen independent. In androgen-dependent cases prostatic cells have more affinity to DTH. In the case of androgen-independent cases the maintenance and survival of cancer cell by various cellular pathways in an androgen-depleted state [13]. Besides, development and survival of pathogenic conditions of a cell there many molecular pathways playing a major.

Treatment of prostate cancer is attributed or attenuated by many processes, which includes Androgen deprivation therapy, chemotherapy and surgical removal of carcinoma (radical prostatectomy). Though there are so many drugs include 5 alpha reductase inhibitors, androgen receptor inhibitors, and various surgical approaches were available to treat prostate cancer [14]. they all has its own side effects or creating secondary complications. For example, 5 alpha reductase inhibitors such as finasteride and dutasteride inhibiting 5 alpha reductase, thereby it controls or limits the production of DTH. Despite prostate Cancer Prevention trial reporting a contrasting data that treating with 5 alpha-reductase inhibitors may alter androgen milieu thereby it cause more frequent aggressive tumor of Gleason's score (7-10) [15]. and prostate cancer treatment cause erectile dysfunction [16]. Above described scenarios were turned researchers towards drug development from natural substances to avoid secondary complications. However, the role of natural substance on prostate cancer treatment is still unclear.

Bioactive compounds were rich fruits and vegetables play a beneficial role against chronic diseases includes cancer, heart diseases, diabetes [17]. For exploring therapeutic efficacy of bioactive compounds derived from a natural substance like fruits, vegetables, herbs, etc. for treating cancer researchers needed a relevant cancer model for testing a suitable bioactive compound as a drug and compared its efficacy with commercially available drugs. More than a decade researchers were working with prostate cancer model (and apply these models for novel drug discovery process [18].

Prostate cancer models

In a prostate cancer research, developing a reliable model is very necessary for one to understand the cellular and molecular mechanism behind initiation, development, and metastasis of prostate cancer. More than a year researchers were developing variously in vivo models includes by chemical induction, hormonal induction or both chemical and hormonal induction, xenograft, transgenic models [19,20,21]. The above-mentioned models have been more close to a clinical condition for developing therapeutic agents. It is familiar that for studying molecular mechanisms of prostate cancer and role of oncogenes and developing novel drug agents against prostatic cancer, researchers were used genetically engineered mice and xenograft models [21]. But cellular and molecular mechanism behind prostate cancer is a complex scenario.

For understanding this complex mechanism, individual gene knockout studies may not be reliable; likewise, there is a lacuna in using xenograft models through subcutaneous injection of the prostate cancer cell. Because in clinical prostate cancer condition, not only the prostatic epithelium involved in process pathogenesis but also associated cellular components like stromal cells, macrophages, neuroendocrine cells, etc. [22]. reported that cancer cells interacting with elements in the stroma of tumor microenvironment such as fibroblast, myofibroblast, blood cells, neuroendocrine cells, etc. These interactions play a major role in cancer biology. In xenograft mouse model genetically engineered model and syngeneic mouse model exhibit interactions between cancer and stromal cells, but it is notable that xenografts mouse is immunodeficient [23].

Due to the heterogeneity of prostate cancer, the creation of metastatic mouse model or advanced prostate cancer model creation is a challenging phenomenon because it is hormone refractory disease[24] or metastatic lesions to the bone, lung, liver and nearby lymph nodes [25,26,27]. So the limitations are there in using those models because of above-mentioned reasons.

Prostate cancer model has been created by using chemical carcinogens, which includes 7,12-Dimethylbenz[a]anthracene (DMBA), Benzo[a]pyrene (B[A]P), 3,2'-dimethyl-4-aminobiphenyl, N-nitrosobis(2-oxopropyl)amine,2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) and N-Methyl-N-nitrosurea

(MNU). The incidence of tumor occurs around 40-60 weeks, by chemical carcinogen followed by testosterone supplements[28]. In prostate carcinogenesis, steroid hormones such as testosterone and estrogen play a major in its pathogenesis. Acting through androgen receptor, testosterone acts as a strong promotor of tumor prostate cancer pathogenesis [29].

N-methylN- nitrosurea (MNU) and 3,2'-dimethyl-4-aminobiphenyl (DMAB) were DNA modifying agents along with steroid hormones like testosterone and estrogen causing prostatic lesions in various strains of rats. MNU and DMAB followed by testosterone supplement induce a high incidence of adenocarcinoma in the dorsolateral and anterior lobe of rat prostate. In this model, the incidence rate is 75% developed around 52 weeks and tumor incidence restricted to targeted site [30,31,32].

Likewise, a study was done by Waalkes et al., [34]. by using a single subcutaneous injection of cadmium chloride of varying dose from low to high i.e. 1, 2, 4, 8, 16, 32 µmol/kg administrated to 10 weeks old Noble rats. At the end of the experimental period of 72 weeks, the prostatic tissues were examined. In that, lower doses received rat exhibited intraepithelial hyperplastic lesions in dorsolateral prostate. A higher dose prostate gland is near normal due to testicular toxicity includes tubular generations, mineralization, and Leydig cell tumors. This might be due to damage to Leydig cells leads to endogenous disruption of testosterone [35].

For creating a prostate cancer model by using MNU as a chemical carcinogen and testosterone propionate as a hormonal supplement[36]. Our experience in this model creation showed high mortality and one of the key observations in postmortem was urinary incontinence. Histology showed glandular hyperplasia with marked infiltrations in prostate and spermatogenic arrest.

Conclusion

Based on these data it was clear many types models are used for different aspects of prostatic cancer research. Each model has its own advantages and disadvantages. Experimental animal models usage for prostate cancer has been able to generate significant information towards understanding the pathobiology. Literature indicates that, at this point of time there is no absolute prefect animal model which could cover all the pathology associated with clinical scenario. However, it will be important to make use of these models to develop improved methods of preventing, detecting and treating human prostate cancer [37]. (Ittmann et al., 2013). Model creation for a prostate cancer is still a challenging phenomenon and a developing process. Thus data generated through animal model study in this branch seems to be intriguing confront in terms of model and therapeutic outcome for that may be model specific.

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Conflict of Interest

Authors declare no conflict of interest.

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