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Growth factors mediated cell signalling in prostate cancer progression: Implications in discovery of anti-prostate cancer agents

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ABSTRACT

Cancer is one of the leading causes of mortality amongst world's population, in which prostate cancer is one of the most encountered malignancies among men. Globally, it is the sixth leading cause of cancer-related death in men. Prostate cancer is more prevalent in the developed world and is increasing at alarming rates in the developing countries. Prostate cancer is mostly a very sluggish progressing disease, caused by the overproduction of steroidal hormones like dihydrotestosterone or due to over-expression of enzymes such as 5-α-reductase. Various studies have revealed that growth factors play a crucial role in the progression of prostate cancer as they act either by directly elevating the level of steroidal hormones or upregulating enzyme efficacy by the active feedback mechanism. Presently, treatment options for prostate cancer include radiotherapy, surgery and chemotherapy. If treatment is done with prevailing traditional chemotherapy; it leads to resistance and development of androgen-independent prostate cancer that further complicates the situation with no cure option left. The current review article is an attempt to cover and establish an understanding of some major signalling pathways intervened through survival factors (IGF-1R), growth factors (TGF-α, EGF), Wnt, Hedgehog, interleukin, cytokinins and death factor receptor which are frequently dysregulated in prostate cancer. This will enable the researchers to design and develop better therapeutic strategies targeting growth factors and their cross talks mediated prostate cancer cell signalling.

1. Introduction

Prostate cancer is the most widespread oncological dilemma with issues concerning the diagnosis, staging and treatment selection [1]. It is one of the common types of malignant disease in the world with worldwide detection of more than 8,90,000 cases and over 2,58,000 deaths each year [2]. The leading cause of deaths from prostate cancer appears to be due to its metastatic nature that in no time progresses into hormone refractory or castrate-resistant stage [3]. Prostate cancer is the most widespread cancer amongst men in the Western world, with the uppermost incidence and the second highest mortality rate of malignancies [4]. It was the sixth most frequently diagnosed cancer among males during 2008 in the Asia–Pacific region, beside cancers of the lung, stomach, liver, colorectal and oesophagus [5].

2. Prostate cancer and current anti-prostate cancer agents

The genetic preferences, inflammation and increased cell proliferation are some of the pre-determinant factors for prostate cancer initiation. The occurrence of these processes in the normal prostate epithelium initiates a cascade of events that lead to the formation of lesions. These formed lesions can either directly progress to primary prostate cancer or proliferative inflammatory atrophy (PIA), which can also induce an intermediate stage called prostatic intraepithelial neoplasia (PIN), in which basal cell layers loses proliferation capacity and further results in advance increase activity of luminal secretory cells (Fig. 1).Prostate cancer progression depends on the decrease of androgen level until an entirely androgen-independent cancer is formed. Molecular and

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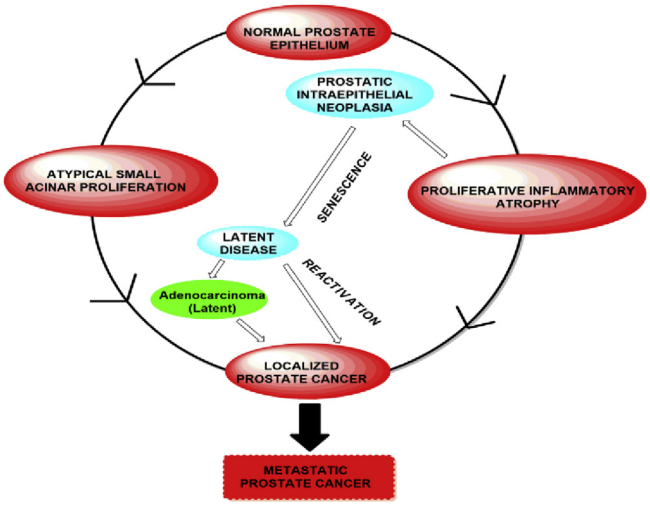

Fig. 1. Representation of stages leading to development of prostate cancer.

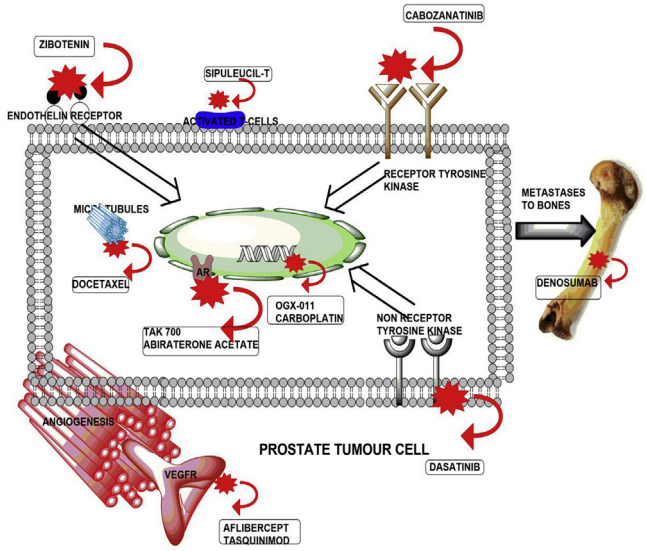

Fig. 2. Drugs along with their molecular targets in prostate cancer.

pathological analysis of human prostate cancer samples and animal model-based studies have shown that infectious agents, estrogenic hormones to dietary carcinogens, age, race, genetics and other occupational factors can cause damage to the prostate epithelium and elicit inflammatory responses leading to chronic or recurrent condition of prostate cancer [6]. Various molecular alterations and pathophysiological factors which affect prostate cancer advancement are briefly summarized in Table 1 [7].

The high mortality rate in prostate cancer in spite having a large number of drugs available for treating the same clearly indicates that chemoprevention must be considered at a new level. It should be based on new theories that influence the growth factors rather than traditional hormone dependency of prostate cancer [8]. In most of the patients, prostate cancer is restricted to a small are and, therefore, can be successfully treated by either radiotherapy or surgery. But the situation becomes typically different and multi-faceted when there is a metastasis. Conventionally, androgen deprivation therapy (ADT) is employed, but owing to resistance, its use has diminished in the recent times [9]. The only alternative, thus, is the castration of androgen glands, but this is also not devoid of several risks factors and side effects [10]. Castration of androgen gland further leads to another class of prostate cancer called castration-resistant prostate cancer (CRPC) [11–13]. Patients with CRPC are left with an even lesser number of treatment options which further complicates the situation [14]. In 2004, a study conducted by Tannock et al. showed that docetaxel could slow down the disease progression and prolong the CRPC patient survival [15]. Studies conducted on docetaxel suggested that it could only lengthen the life span of such patients for merely 3–4 months.

Some the drugs which inhibits important molecular targets involved in the progression of prostate cancer are portrayed in Fig. 2. In addition to it United States Food and Drug Federation (USFDA) approved drugs for the treatment of prostate cancer along with their some chemical structures (Fig. 3) are collected in Table 2. Many of these approved drugs suffer from common problems such as resistance and complicated side effects like bowel dysfunction, urinary dysfunction, erectile dysfunction, related heart functions etc., Therefore there is an urge and extreme need for the clinical development the better novel therapeutics that can be practical in slowing down the progression of prostate cancer [14,16–18].

Natural products are also reported to be used in treating prostate cancer and various other types of tumours [34]. The majority of chemical molecules have been reverted to the use of natural products because of their safety, less toxicity, antioxidant properties [35]. Extensive research over the history has identified

Table 1
Factors involved in the development and advancement of prostate cancer [7].

Pathophysiological processes	Genetics alterations	
Genetic preference, Inflammation, Increased proliferation index	Mutations in hereditary prostate cancer1 (HPC1); hereditary prostate cancer 2 (HPC2); ribonucleaseL (2′,5′ oligoisoadenylate synthetase dependent (RNASEL); breast cancer 2 (BRCA2), macrophage scavenger receptor 1 gene (MSR1)	***ANDROGEN INDEPENDENCE***
Proliferation abnormalities, Lower apoptosis index, Telomerase shortening, Oxidative DNA damage, Aberrant gene expression	Loss of heterozygosity, changes on chromosomes 7 and 8, bcl-2 overexpression, glutathione-S-transferase π, alpha-methylacyl-CoA racemase (AMACR) overexpression, androgen receptor signalling down-regulation	
Loss of basal cell differentiation, cell signalling pathways	Loss of hemidesmosome forming proteins and adhesive molecules, oncogenic activation	
Local invasion, migration and Resistance to the immune system, Transmigration	Osteopontin overexpression, miRNAs differential expression, E-cadherin downregulation	
Androgen independent epidermal to mesenchymal transition	EZH2 overexpression	