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Review Article

Tumor models for prostate cancer exemplified by fibroblast growth factor 8-induced tumorigenesis and tumor progression

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ABSTRACT

Prostate cancer is a very common malignancy among Western males. Although most tumors are indolent and grow slowly, some grow and metastasize aggressively. Because prostate cancer growth is usually androgen-dependent, androgen ablation offers a therapeutic option to treat post-resection tumor recurrence or primarily metastasized prostate cancer. However, patients often relapse after the primary response to androgen ablation therapy, and there is no effective cure for cases of castration-resistant prostate cancer (CRPC). The mechanisms of tumor growth in CRPC are poorly understood. Although the androgen receptors (ARs) remain functional in CRPC, other mechanisms are clearly activated (e.g., disturbed growth factor signaling). Results from our laboratory and others have shown that dysregulation of fibroblast growth factor (FGF) signaling, including FGF receptor 1 (FGFR1) activation and FGF8b overexpression, has an important role in prostate cancer growth and progression. Several experimental models have been developed for prostate tumorigenesis and various stages of tumor progression. These models include genetically engineered mice and rats, as well as induced tumors and xenografts in immunodeficient mice. The latter was created using parental and genetically modified cell lines. All of these models greatly helped to elucidate the roles of different genes in prostate carcinogenesis and tumor progression. Recently, patient-derived xenografts have been studied for possible use in testing individual, specific responses of tumor tissue to different treatment options. Feasible and functional CRPC models for drug responsiveness analysis and the development of effective therapies targeting the FGF signaling pathway and other pathways in prostate cancer are being actively investigated.

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1. Introduction

The prostate is a secretory organ; it produces approximately 20% of the seminal fluid. Prostatic secretion contributes to sperm function, but is not mandatory to the fertilizing capacity of sperm. Prostatic diseases are very common, and they include acute and chronic inflammation, benign prostatic hyperplasia (BPH) with associated lower urinary tract symptoms, and prostate cancer. The lifetime risk of prostatic adenocarcinoma is approximately 10% for men in Western countries.

1.1. *Natural history of prostate cancer*

Progression of prostate cancer is a multistep process, and its mechanisms are poorly understood. Prostate cancer usually occurs in the peripheral zone [1], while BPH often occurs in the transition zone of the prostate. Commonly occurring chronic inflammation [2] may predispose the tissue to the development of malignant changes, although the concept that inflammation can promote prostate cancer is still highly speculative. Prostatic intraepithelial neoplasia (PIN) is considered a precursor of prostate cancer. In low-grade PIN (LG-PIN), the epithelial cells grow in multiple layers that project into the lumen of the gland, although the basal cell layer is still intact. In high-grade PIN (HG-PIN), the basal layer has been described as discontinuous [3]. HG-PIN resembles differentiated adenocarcinoma, and it is commonly found in radical prostatectomies. HG-PIN and prostate cancer share many genetic abnormalities. Also, the location of HG-PIN in the peripheral zone of the prostate is similar to the location of prostate cancer.

Prostate cancer can be screened by means of the prostate-specific antigen (PSA) test; however, the actual cancer diagnosis is based on the histological or cytological examination of biopsy samples. The most common method to predict the behavior of adenocarcinoma of the prostate is the Gleason score [4]. In this grading system, the morphology and organization of the prostatic glands are histologically assessed. The score is distributed from 2 to 10, and 2 represents the least aggressive form.

The rate of latent carcinomas found in autopsies of patients that died because of reasons other than cancer increases with age [5,6]. Microscopic lesions are found in 70–80% of men over 80 years of age. At diagnosis, prostate cancer is most often restricted to the prostate. Early stage prostate cancer can usually be successfully treated with surgical prostatectomy and radiotherapy, or it may be left under watchful waiting. Only 10% of prostate cancers develop to clinical disease, and careful monitoring is often the first choice of treatment [5]. Younger men with poorly differentiated prostate cancers are treated more intensively [7]. If the tumor cells have invaded outside the prostatic capsule, androgen ablation therapy can be used to prevent tumor growth and further spread. Androgen ablation therapy has been used for more than 60 years [8] and is often combined with radiotherapy. Most (70–80%) patients treated with hormone therapy get relief from their symptoms, and side effects are mild compared with other cancer therapies [5].

The effects of hormone therapy may last for a number of years and improve the quality of life and survival of prostate cancer patients. Eventually, metastatic prostate cancer develops to the final, castration-resistant stage [9], for which there is no cure available and only palliative therapy can be given. Bone pain can be relieved using bisphosphonate, denosumab, or radiopharmaceutical radium-223 chloride treatment [10–12]. Until recently, chemotherapy has not been considered an effective treatment against prostate cancer; however, studies with docetaxel alone or combined with the estradiol derivative estramustine, the CYP17 inhibitor abiraterone acetate, and the androgen receptor (AR) antagonist enzalutamide demonstrated promising results against castration-resistant prostate cancer (CRPC) [13–16]. New investigational drug compounds such as the AR inhibitor ODM-201 and the taxane analog cabazitaxel have also shown promising results in clinical trials [17,18]. Although these agents can extend the survival of CRPC patients, CRPC remains incurable, and new therapies are needed [17,19–21].

1.2. *Hormone and growth factor regulation*

Androgens are essential for the prostate to maintain its normal morphology and function. They also have a central role in the development of benign prostatic hyperplasia and prostate cancer. Many androgen effects are mediated through paracrine and autocrine molecules, including growth factors and their receptors. Important components in prostate cancer progression are angiogenic growth factors, which induce the sprouting of new capillaries to ensure the availability of oxygen, glucose, and nutrients for the growing tumors [22]. The angiogenic switch is dependent on the balance between angiogenic factors (e.g., vascular endothelial growth factor (VEGF), fibroblast growth factors (FGFs), angiopoietins, transforming growth factors (TGFs), platelet-derived growth factor (PDGF), tumor necrosis factor α (TNF-α), interleukins, and chemokines) [23,24] and anti-angiogenic factors (e.g., thrombospondin, endostatin, tumstatin, and vasostatin) [22]. Oncogenes, tumor suppressor genes, and external factors such as hormones and (most importantly) hypoxia can also affect the balance between angiogenic and anti-angiogenic factors [23,25–27]. Angiogenic stimulation is low in normal cells; however, tumors greater than 2 mm in diameter are dependent on the ability of the tumor cells to induce and maintain neovascularization in tumor tissue [28]. Tumor metastasis is also dependent on angiogenesis. Tumor angiogenesis is often uncontrolled and results in chaotic and heterogeneous vascularization, which may lead to metabolic changes and decreased oxygen and glucose concentrations. Consequently, hypoxia is a common feature of solid tumors. Hypoxia affects the growth and spread of tumors; hypoxic tumors are also more resistant to radiotherapy and chemotherapy [29].

2. Animal models of prostate cancer

Although prostate cancer is the most common cancer in human men, it rarely occurs in other animal species. An optimal animal model should mimic the key features of human prostate adenocarcinoma, such as an initial response