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Review

Multidimensional approaches in dealing with prostate cancer

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Abstract

Prostate cancer is one of the most prevalent malignancies worldwide affecting the human male population. Different case-control, cohort or twin studies and segregation analyses point towards the presence of prostate cancer-susceptibility genes in the population. The studies have shown linkage of prostate susceptibility genes to multiple loci on chromosome 1 and single locus each on chromosomes 4, 8, 16, 17, 19, 20 and X chromosome. However, differences right from the mode of inheritance (autosomal dominant or X-linked recessive) to the target genes exist. There have been reports supporting no or weak linkage to these loci as well. Also, region (environmental factors), age and dietary habits have implications in different aspects of the disease. The important targets for treating prostate cancer are androgens and estrogen (synthesized from androgens by the action of enzyme aromatase) owing to their involvement in development and progression of prostate cancer. Further, prostate gland needs androgens (male hormones) for its normal maintenance and functioning. Besides, radiation therapy and surgical methods have also been used. The emerging areas include identifying and preparing successful vaccines from candidate peptides and gene therapy in several forms. This review deals with the paradox of linkage analyses and the various approaches in practice for treatment and management of prostate cancer.

Keywords: Linkage; Androgen; Estrogen; Radiation

1. Introduction

In any given living system, cell division and cell death are well orchestrated processes to cope up with various physiological, biochemical and environmental challenges and to maintain homeostasis. Regulation of cell cycle at the highest possible stringency level is an integral part for successful survival of any living system. Deviation in any of these mechanisms to the slightest level may result in cancer (uncontrolled cell growth) or other malignancies. There are different genetic aspects involved in different types of cancer with the underlying principle being loss of control over cell division.

The prostate gland develops by the 9th week of embryonic life and is the modified wall of the proximal portion of the male urethra. Thereafter, the mesenchyme, urethra and Wolffian ducts condense to give rise to the adult prostate gland. Its main function is to store and secrete a clear, slightly alkaline fluid that constitutes up to 1/3rd volume of the seminal fluid. It also contains some smooth muscles that help expel semen during ejaculation. It needs androgens (male hormones) for its proper maintenance and function. The main male hormone,

Abbreviations: AR, androgen receptor; ARE, androgen response element; CaP, carcinoma of prostate; CBP, Creb-Binding Protein; CPA, cyproterone acetate; CT, computed tomography; EDT, estrogen deprivation therapy; ER, estrogen receptor; GM-CSF, granulocyte macrophage colony-stimulating factor; HPCX, hereditary prostate cancer, X-linked; HPC, hereditary prostate cancer; IMRT, intensity-modulated radiation therapy; LOD, logarithm of the odds (to the base 10); MAB, maximal androgen blockade; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; MRSI, magnetic resonance spectroscopy imaging; PAP, prostatic-acid phosphatase; PCa, prostate cancer; PCAP, predisposing for prostate cancer; PIN, prostate intraepithelial neoplasia; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; SRC1, steroid coactivator 1; TRAMP, transgenic adenocarcinoma of the prostate.

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testosterone, is produced primarily by testicles and in small amounts by the adrenal glands. Owing to the important role of androgens in maintenance and functioning of prostate gland they are supposedly key players in PCa as well (Fig. 1).

Prostate cancer (PCa) or carcinoma of prostate (CaP) is one of the most prominent cancers affecting the human male population around the world. A man has a 1/5 chance of developing PCa during his lifetime (Feuer, 1997). Notable regional differences have been observed in the populations in the prevalence of PCa with its occurring frequency highest in the African Americans and lowest in the Asian populations (Whittemore, 1994). Studies on familial clustering of PCa have shown an increased risk of an individual with several affected first-degree relatives or with an affected brother who had an early age at onset and about 9% of cases are expected to occur in families with several affected family members (Carter et al., 1992). The role of environmental factors in PCa has also been studied which highlighted the importance of immigration (Dunn, 1975), lifestyle and dietary habits (Whittemore et al., 1995). Apart from these factors, age is also a primary risk factor in PCa occurrence with incidence per 100,000 increasing from 34 to 150 to 440 in American Caucasian men of age 60, 70 and 80 years, respectively (Kosary et al., 1995).

PCa is expected to be diagnosed in 15% of the men in the United States. Also, results of autopsy studies suggest that 30% of the men of age > 45 years may have prostate lesions that can be histologically identifiable as PCa (Kosary et al., 1995; Dhom, 1983). There is a good chance that these lesions remain latent for the person's lifetime but what actually triggers some of them to become biologically active metastatize and manifest as a potentially lethal disease remains a mystery till date though a genetic role is very strongly suggested. Different types of studies with variable but reasonable sample size have been done to understand the genetics of PCa. These include case-control, cohort and twin studies as well as segregation analyses. All the results point towards existence of prostate cancer-susceptibility genes in the population but there is difference in the suggested modes of inheritance. Three independent segregation analyses support an autosomal dominant mode of inheritance. Dominant alleles with a population frequency of 0.36%–1.67% are supposed to account for ~9% of all PCa cases at age ≤ 85 years and ~43% cases at age ≤ 55 years (Carter et al., 1992). In contrast to this data from two studies are most consistent with an X-linked or recessive model of inheritance (Monroe et al., 1995; Narod et al., 1995). Studies have indicated linkage of prostate susceptibility genes to multiple loci on chromosome 1 and single locus each on chromosomes 4, 8, 16, 17, 19, 20 and X chromosome.

2. The loci involved

2.1. 1q24–25(HPC1)

There have been number of studies indicating evidence for linkage to regions that may contain disease susceptibility loci for PCa. Smith et al. (1996) proposed the first such locus on chromosome 1q24–25 termed hereditary prostate cancer 1 (HPC1) and was supposed to account for the disease in 34% families with PCa in a data set defined by families with three or more first-degree affected relatives, PCa in three or more generations or two affected siblings diagnosed at age ≤ 60 years. Another study (Xu J and the International Consortium for Prostate Cancer Genetics, 2000) of 772 families suggests that 6% of families with hereditary prostate cancer have linkage to HPC1. The chances of having linkage to HPC1 locus is enhanced in families with an early mean age at diagnosis (<65 years), four or more close relatives with the disease and proportionately more advanced stage disease (Grönberg et al., 1997; Grönberg et al., 1999). Apart from these, there have been several weak evidences confirming the linkage to HPC1 (Cooney et al., 1997; Hsieh et al., 1997). What's startling is the contrasting report about the same locus. McIndoe et al. (1997) studied 49 high risk prostate cancer families and found

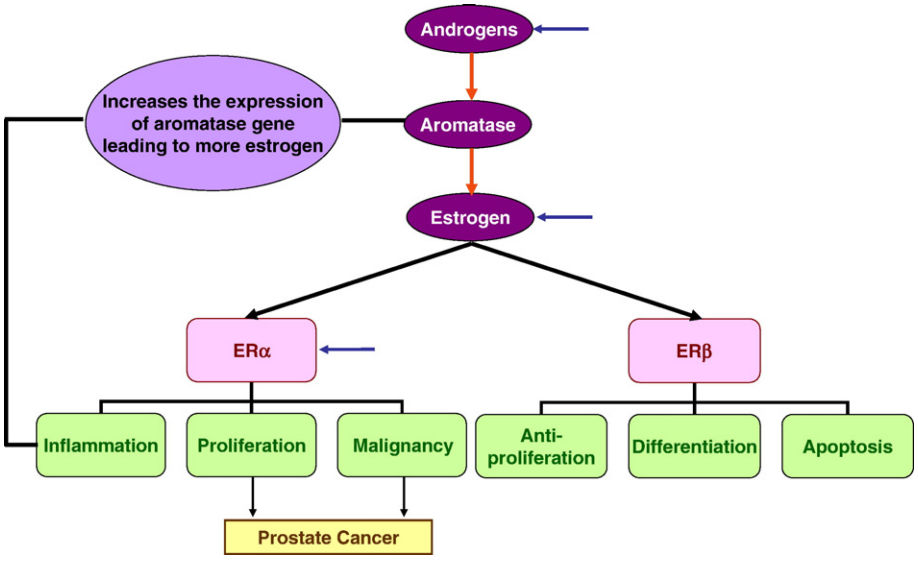

Fig. 1. The role of androgens and estrogens in prostate cancer. Blue arrow indicates the targets for treatment of prostate cancer.