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Review

Genetic variation: effect on prostate cancer ☆

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ABSTRACT

The crucial role of androgens in the development of prostate cancer is well established. The aim of this review is to examine the role of constitutional (germline) and tumor-specific (somatic) polymorphisms within important regulatory genes of prostate cancer. These include genes encoding enzymes of the androgen biosynthetic pathway, the androgen receptor gene, genes that encode proteins of the signal transduction pathways that may have a role in disease progression and survival, and genes involved in prostate cancer angiogenesis. Characterization of deregulated pathways critical to cancer cell growth have lead to the development of new treatments, including the CYP17 inhibitor abiraterone and clinical trials using novel drugs that are ongoing or recently completed [1]. The pharmacogenetics of the drugs used to treat prostate cancer will also be addressed. This review will define how germline polymorphisms are known affect a multitude of pathways, and therefore phenotypes, in prostate cancer etiology, progression, and treatment.

Contents

1. Introduction

Prostate cancer is the most frequently diagnosed cancer, and the second leading cause of death from cancer among men in the United States. The disease is more frequent in older men and is associated with a higher incidence in certain racial/ethnic backgrounds. African

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Americans have the highest frequency of prostate cancer worldwide, while Caucasians, Hispanics, and Asians respectively have the next highest risk in the United States [2]. Native Asian men historically have the lowest prostate cancer incidence in the world [3] although much of this difference may be due to differences in detection strategies used in various countries [4]. Racial identity is a strong predictor of an individual's risk of prostate cancer, and migration to Western countries further increases risk within racial groups [5]. Using epidemiological data, it appears that there is a significant influence of genetic background in prostate carcinogenesis, and the genetic impact is most important in the context of environmental/lifestyle influences [6].

As there are many factors that influence disease etiology, inherited prostate cancer risk is often difficult to ascertain. Over the past decade, disease susceptibility and aggressiveness loci have been reported, and the risk of developing prostate cancer is significantly increased in certain families. However, rare highly penetrant loci explain only a small percentage of the overall number of cases of prostate cancer, with most cases being of a sporadic nature (~75% of prostate cancers) [7]. Rather common low-penetrance alleles in multiple genes may be even more important in determining prostate cancer risk in most individuals, and might also be related to familial prostate cancer [8,9]. The androgen biosynthetic pathway, the androgen receptor (AR), and downstream AR effector pathways (Fig. 1) are genetically polymorphic, and many such polymorphisms have been linked to prostate cancer etiology and treatment. Moreover, somatic mutations in prostate cells also increase the ability of prostate cancer to increase in aggressiveness and ultimately evade treatment. The aim of this review is to examine the role of constitutional (germline), and tumor-specific (somatic) polymorphisms (including single nucleotide polymorphisms (SNPs) at or within candidate genes for prostate cancer, genes that encode enzymes of the androgen biosynthetic pathway, the AR gene and proteins of the signal transduction pathway which may have a role in disease progression and survival.

2. Androgen biosynthetic pathways and the androgen receptor

Although many factors may contribute to the underlying biology and clinical course of prostate cancer [10], it is thought that genetic variation in androgen biosynthesis and signaling genes most likely influence the eventual outcome of the disease. This section will summarize investigations into inherited inter-individual variability in the most studied androgen biosynthesis genes: *CYP17*, *SRD5A2*, and *AR*.

2.1. CYP17

Localized within the liver, testis, and adrenal cortex, CYP17 catalyzes the formation of several products in the androgen biosynthetic pathway (Fig. 1). It converts pregnenolone into 17α-hydroxypregnenolone and 17α-hydroxyprogesterone (17α-hydroxylase activity) and both of these products into dehydroepiandrostanedione (DHEA) and androstanedione, the major circulating steroid hormone precursors (17,20-lyase activity). Abiraterone, TOK-001, TAK-700, and ketoconazole all inhibit this pathway.

Individuals with prostate disease comprising many different racial backgrounds have been genotyped for various *CYP17* alleles, although most studies have focused on the A1/A2 allele (rs743572). The A1/A2 allele encodes a T > C transition that results in the formation of a CCACC Sp-1 promoter site 34 base pairs upstream of *CYP17* that changes a *Msp1a* restriction site designating either the 'A1' or 'A2' alleles [11]. However, the nucleotide change in the Sp-1 promoter site does not

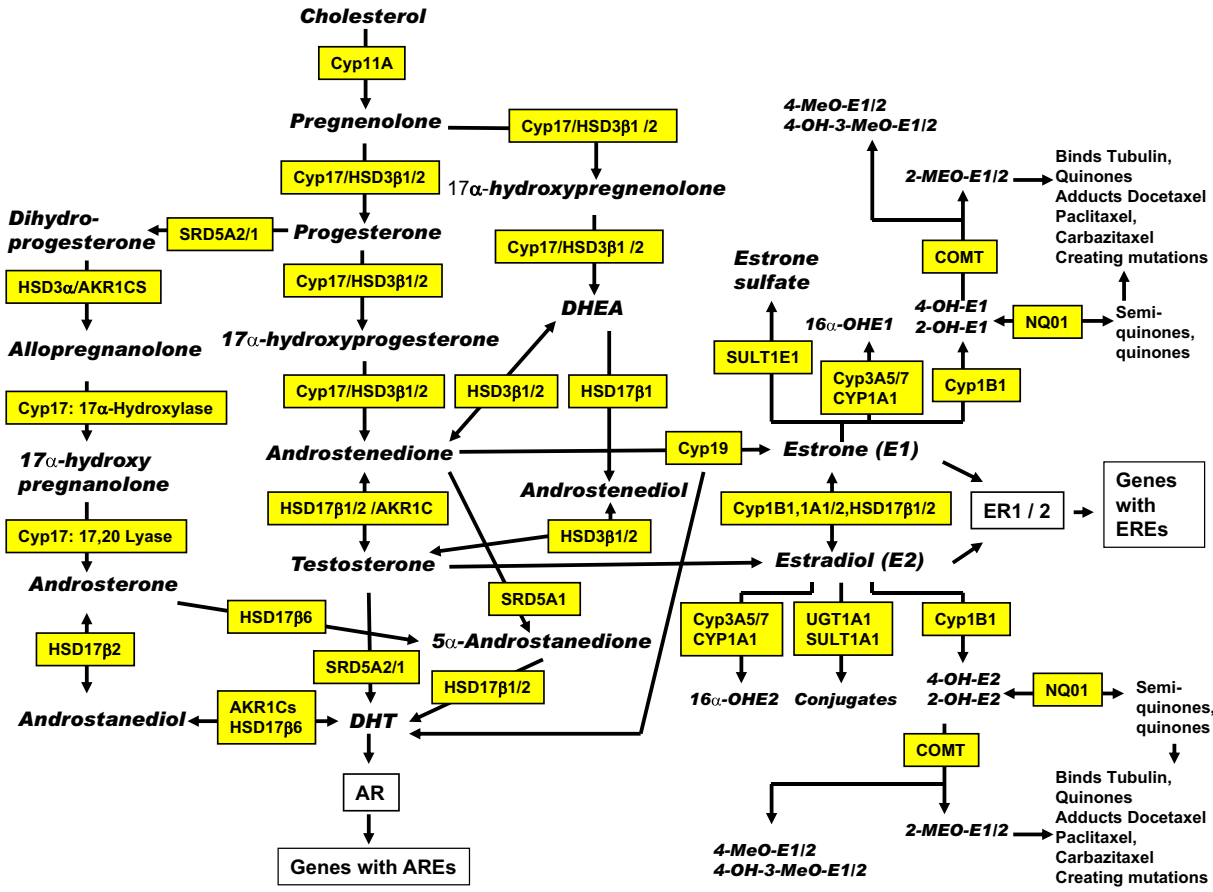

Fig. 1. Sex hormone biosynthesis and degradation pathway.