Molecular and Cellular Endocrinology 360 (2012) 68–75

Contents lists available at SciVerse ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

Review

Putting the brakes on continued androgen receptor signaling in castration-resistant prostate cancer

Andrew Eichholz *, Roberta Ferraldeschi, Gerhardt Attard, Johann S. de Bono

Institute of Cancer Research, 15 Cotswold Road, Sutton, Surrey SM2 5NG, United Kingdom

ARTICLE INFO

Article history:
Available online 1 October 2011

Keywords:
Abiraterone
Orteronel (TAK-700)
VN/124-1 (TOK-001)
MDV3100
Heat shock proteins
OGX-427

ABSTRACT

Patients with advanced prostate cancer initially respond very well to medical or surgical castration. Despite a good initial response, the disease progresses to a castration-resistant state. Castration-resistant prostate cancer (CRPC) remains addicted to androgen receptor signaling. The addition of conventional anti-androgen agents, such as bicalutamide, only provides a transient benefit. This has led to a search for further drug targets. Cytochrome P450 17 (CYP17) is an enzyme that is vital for the adrenal biosynthesis of androgens. The CYP17 inhibitor abiraterone acetate has a proven benefit in a phase III randomized trial and other CYP17 inhibitors are currently being evaluated. The novel antiandrogen MDV3100 is a small molecule androgen receptor antagonist with promising activity. Heat shock proteins (HSPs) bind to the androgen receptor and modify its activity. Several HSP inhibitors are under evaluation in clinical trials. This review explores the role of CYP17 inhibitors, MDV3100, and HSP inhibitors.

Contents

Abbreviations: AAG, 17-*N*-allylamino-17-demethoxygeldanamycin; ACTH, adrenocorticotropic hormone; AR, androgen receptor; cAMP, cyclic adenosine monophosphate; CREB, cAMP response element-binding; CRPC, castration-resistant prostate cancer; CYP, cytochrome P450; DHEA, dehydroepiandrosterone; EYFP, enhanced yellow fluorescent protein; GnRH, gonadotropin-releasing hormone; HSF, heat shock factor; HSP, heat shock protein; LH, luteinizing hormone; MAPK, mitogen-activated protein kinase; NCoR, nuclear hormone receptor corepressor; PTEN, phosphatase and tensin homolog; siRNA, small interfering RNA; SMRT, silencing mediator of retinoid.

* Corresponding author. Address: Male Urological Cancer Research Centre, Institute of Cancer Research, 15 Cotswold Road, Sutton, Surrey SM2 5NG, United Kingdom. Tel.: +44 20 8722 4366; fax: +44 20 8722 4084.
E-mail address: Andrew.Eichholz@icr.ac.uk (A. Eichholz).

0303-7207/$ - see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.mce.2011.09.038

1. Introduction

The treatment of advanced prostate cancer poses a significant challenge. Seventy years ago, Huggins and Hodges first demonstrated that prostate cancer responds to androgens. Androgen deprivation could cause a decrease in serum acid phosphatase (suggesting regression of bony metastases) whilst administering injections of androgens had the opposite effect (Huggins and Hodges, 1941).

Testosterone and other androgens are produced primarily in the testes. This production is under endocrine control. The hypothalamus produces gonadotropin-releasing hormone (GnRH) that stimulates the pituitary gland to produce luteinizing hormone (LH). This in turn causes the Leydig cells of the testes to produce testosterone and dihydrotestosterone from cholesterol via a biosynthetic pathway (Fig. 1). Cholesterol is converted to progestagens that are then converted to the androgens dehydroepiandrosterone (DHEA), DHEA-sulfate and androstenedione. Testosterone is produced by conversion from DHEA or androstenedione by the action of

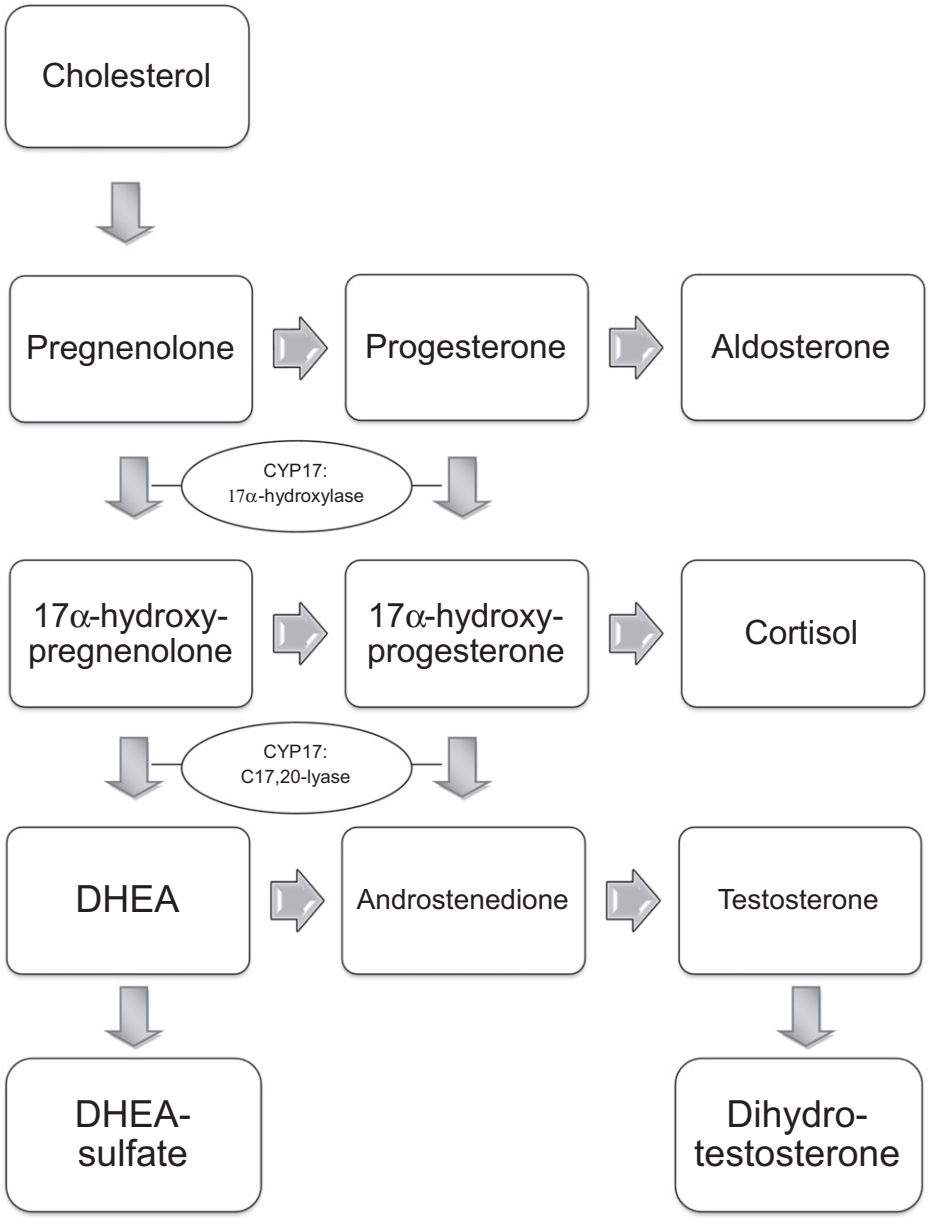

Fig. 1. Androgen biosynthesis pathway. CYP17 has 17α-hydroxylase and C17,20-lyase activity which is necessary for androgen production. CYP, cytochrome P450; DHEA, dehydroepiandrosterone.