Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Steroid Biochemistry & Molecular Biology 92 (2004) 219–220
The Journal of Steroid Biochemistry & Molecular Biology
www.elsevier.com/locate/jsbmb

Preface

Steroids and prostate cancer

Prostate cancer is the most common malignancy among men in many European and North American countries. It is also one of the most common causes of cancer related death. The incidence of prostate cancer has increased rapidly during the last decades, which is partly explained by the improved diagnostic tools, especially the use of serum prostate specific antigen (PSA) measurements to screen asymptomatic men for the cancer. The etiology, risk factors and molecular mechanisms of prostate cancer are poorly understood. However, strong evidence supports the idea that steroid hormones, especially androgens, play crucial roles in the development and progression of prostate cancer.

This issue of Journal of Steroid Biochemistry and Molecular Biology is a compilation of reviews on steroid hormones, prostate and prostate cancer. First, Cunha et al. give an overview on the organogenesis of the prostate gland. The significance of epithelial–stromal interactions in normal and neoplastic growth is emphasized. Subsequent reviews concentrate more specifically on the steroid hormones and their receptors. The prostate is a hormone target organ whose development, growth and function are hormonally regulated, especially by androgens, but also by estrogens. The development of prostate cancer occurs in the context of steroid hormone signaling (see Platz and Giovannucci, this issue), and at least initially the biology of prostate cancers is regulated by androgens. Indeed, hormonal therapy has been the golden standard of treatment for advanced prostate cancer for more than half century (see Tammela, this issue).

Androgens elicit their effects via androgen receptor signaling, which is the topic reviewed by Culig et al. and Linja and Visakorpi (this issue). Progress on the molecular biology of the androgen receptor (AR) has demonstrated a critical association of the AR with co-activator or co-repressor proteins that modulate its activation. In prostate cancers, AR co-activators such as SRC-1 and TIF-2 are up-regulated in patients who failed prostate cancer endocrine therapy. Increased expression of these co-activators is associated with enhanced activation of the AR by the weak adrenal androgen, dehydroepiandrosterone, meaning that ligand specificity is altered. As reviewed by Culig et al. (this issue), it is increasingly apparent that progression of prostate cancer is associated with changes in AR co-activator expression and interactions of the AR with other transcriptional integrators. Another important aspect of the AR is its polymorphisms, especially the length of CAG repeat in exon 1, which is associated with increased risk of prostate cancer (reviewed by Linja and Visakorpi as well as Platz and Giovannucci, this issue). The genetic alterations in AR indicate that AR should be considered as a putative treatment target.

While androgens regulate a plethora of genes during development, growth and function of the prostate, Swinnen et al. (this issue) have focussed on androgenic regulation of genes encoding lipogenic enzymes and have show that androgens coordinately stimulate the expression of lipogenic enzyme genes through interference with the molecular mechanism controlling activation of sterol regulatory element-binding proteins. The resulting increased lipogenesis produces key membrane components (phospholipids, cholesterol), hallmarks of cancer cells. This relationship between lipids and cancer provides the rationale for pharmacologic inhibition of lipogenesis, which induces apoptosis in prostate cancer cell lines and reduces tumor growth in xenograft models. Lipogenesis is a fundamental aspect of prostate cancer cell biology and is a potential target for chemoprevention and therapy of advanced prostate cancer.

While prostate is clearly an androgen target organ, Härkönen and Mäkelä (this issue) emphasize the fact that the prostate is also a target for estrogens by virtue of the expression of estrogen receptor α (ERα) and estrogen receptor β (ERβ) in prostatic stroma and epithelium, respectively. The developing prostate is particularly sensitive to increased levels of endogenous and/or exogenous estrogens. Perinatal exposure of rats and mice to high or low dose estrogens leads to "imprinting" of prostate associated with effects on epithelial proliferation, expression of androgen and estrogen receptors, inflammation and dysplastic epithelial changes later in life. Prolonged treatment of adult rodents with estrogen in combination with androgen elicits epithelial hyperplasia, dysplasia and adenocarcinoma of prostate. Recent studies on selective estrogen receptor modulator (SERM) inhibition of prostate cancer development beyond PIN-type lesions in transgenic mice suggests a role for estrogens in prostate cancer progression and suggests that direct inhibition of estrogen action

0960-0760/$ – see front matter
doi:10.1016/j.jsbmb.2004.10.001

at the level of prostate tissue may provide novel strategies for prostate cancer chemoprevention or therapy. Also, a review by Sorrenson et al. (in this issue) suggests that estrogen influence is increased with a subsequent over-expression of estrogen-regulated genes during malignant transformation of prostate cells.

Finally, the role of Vitamin D in the regulation of prostate cancer is discussed in reviews by Peehl and Feldman, and Lou et al. Peehl and Feldman (this issue) emphasize that Vitamin D, acting through the Vitamin D receptor, has many tumor suppressive functions in the prostate including inhibition of proliferation, induction of apoptosis and/or differentiation, and reduction of cellular invasion. Because of these properties, Vitamin D is being evaluated as an agent to prevent or treat prostate cancer. Lou et al. (this issue) emphasize the importance of Vitamin D metabolism as a factor in development of prostate cancer. Deficiency of 25(OH)-vitamin D is common especially during the winter season in the Northern and Southern latitudes and is associated with increased risk of prostate cancer. Lou et al. (this issue) propose that local metabolism of Vitamin D plays an important role in the development and progression of prostate cancer.

G.R. Cunha*
P. Tuohimaa
T. Visakorpi (Editors)
Medical School, University of Tampere, Finland
*Corresponding author.
Present address: University of California, 3rd and Parnassus, Department of Anatomy, HSW 1323 San Francisco, CA 94143, USA.
E-mail address: grcunha@itsa.ucsf.edu (G.R. Cunha)