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Journal of Steroid Biochemistry & Molecular Biology 92 (2004) 273–279
The Journal of Steroid Biochemistry & Molecular Biology
www.elsevier.com/locate/jsbmb

Androgens, lipogenesis and prostate cancer

Johannes V. Swinnen*, Hannelore Heemers, Tine Van de Sande, Ellen De Schrijver, Koen Brusselmans, Walter Heyns, Guido Verhoeven

Laboratory for Experimental Medicine and Endocrinology, University of Leuven, Campus Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium

Abstract

Both experimental and epidemiological data indicate that androgens are among the main factors controlling the development, maintenance and progression of prostate cancer. Identifying the genes that are regulated by androgens represents a major step towards the elucidation of the mechanisms underlying the impact of androgens on prostate cancer cell biology and is an attractive approach to find novel targets for prostate cancer therapy. Among the genes that have been identified thus far, several genes encode lipogenic enzymes. Studies aimed at the elucidation of the mechanisms underlying androgen regulation of lipogenic genes revealed that androgens coordinately stimulate the expression of these genes through interference with the molecular mechanism controlling activation of sterol regulatory element-binding proteins (SREBPs), lipogenic transcription factors governing cellular lipid homeostasis. The resulting increase in lipogenesis serves the synthesis of key membrane components (phospholipids, cholesterol) and is a major hallmark of cancer cells. Pharmacologic inhibition of lipogenesis or RNA-interference-mediated down-regulation of key lipogenic genes induces apoptosis in cancer cell lines and reduces tumor growth in xenograft models. While increased lipogenesis is already found in the earliest stages of cancer development (PIN) and initially is androgen-responsive it persists or re-emerges with the development of androgen-independent cancer, indicating that lipogenesis is a fundamental aspect of prostate cancer cell biology and is a potential target for chemoprevention and for antineoplastic therapy in advanced prostate cancer.

Keywords: Androgens; Lipogenesis; Prostate cancer; SREBP; Fatty acid synthase

1. Introduction

Prostate cancer is the most commonly diagnosed non-skin malignancy and the second leading cause of cancer-related death in Caucasian males. Epidemiological, experimental and clinical data point to an important role of androgens in the development, maintenance, management and progression of this disease. First, males castrated at an early age do not develop prostate cancer [1,2]. Second, high incidence of prostate cancer has been claimed to be associated with high levels of plasma androgens [3–5]. Third, administration of androgens to laboratory animals enhances the development of prostate cancer [6,7]. Fourth, removal of androgens or blockage of their synthesis induces programmed cell death of prostate cancer cells and leads to a marked regression of the tumor in the majority of patients [8–10]. Based on this androgen-dependence of prostate tumor cells, androgen ablation has become the standard treatment of advanced disease. Unfortunately, most patients relapse because of the outgrowth of androgen-independent cells.

A key player in prostate cancer development and progression is the androgen receptor (AR). Androgens exert most of their effects on prostate cancer cells by binding to and activating the androgen receptor. The AR is a member of the nuclear receptor superfamily and functions as a ligand-dependent transcriptional regulator [11]. The AR promotes the growth and regulation of the normal prostate and remains present in nearly all prostate tumors, even in recurrent androgen-independent tumors [12,13]. In prostate cancers, several alterations in the AR have been found that render the AR more active (e.g. shorter poly-glutamine repeats) or that broaden its ligand-specificity, this way contributing to the escape from androgen ablation therapy, reviewed in [14,15]. Mounting evidence indicates that altered expression of AR coactivators and crosstalk between the AR and other (growth factor and cytokine related) signaling pathways play a central role in the dysregulation of AR function in prostate cancer

* Corresponding author. Tel.: +32 16 345970; fax: +32 16 345934.
E-mail address: johan.Swinnen@med.kuleuven.ac.be (J.V. Swinnen).

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doi:10.1016/j.jsbmb.2004.10.013

resulting in abnormal and sustained expression profiles of AR-regulated genes even after escape from androgen ablation therapy, reviewed in [14,15].

Identifying genes that are affected by androgens in prostate cancer cells and that ultimately mediate the impact of androgens on the development and the progression of the disease is an attractive approach towards the identification of novel biomarkers and targets for chemoprevention or curative therapy, and represents an important effort in the battle against prostate cancer. Using a variety of techniques including mRNA differential display, SAGE and DNA microarray analysis, more than 300 androgen-regulated genes have been identified, covering diverse cellular functions including cell survival and proliferation, differentiated secretory function, transport and trafficking, endoplasmic reticulum stress response, and lipid metabolism [16–20]. In this review we focus on this latter set of genes. We elaborate on the molecular mechanism underlying androgen regulation of lipid metabolism, we discuss the role of lipid metabolism in prostate cancer cell biology and we analyze the potential of lipogenic enzymes as disease markers and as targets for antineoplastic therapy.

2. Lipogenesis as an androgen-regulated process in prostate cancer cells

Since the identification of acyl-CoA-binding protein as an androgen-regulated protein in the widely used LNCaP prostate cancer cell line [19], numerous findings have indicated that lipid metabolism is a major target of androgen action in prostate cancer cells. One of the most direct pieces of evidence was the observation that exposure of LNCaP cells to androgens (both natural androgens such as testosterone and dihydrotestosterone and synthetic androgens such as R1881 and mibolerone) leads to a massive accumulation of neutral lipids (triglycerides and cholesteryl esters), which are storage products of fatty acid and cholesterol, respectively [21]. In support of the involvement of the androgen receptor the androgen antagonist Casodex (bicalutamide) abolished the stimulatory effects of androgens. Moreover, no changes in lipid profile were observed in AR-negative prostatic cell lines. Careful analysis of the origin of the accumulated lipids revealed that these lipid accumulations are the result of a major androgen-induced increase in the synthesis of fatty acids and of cholesterol, the majority of which is used for membrane synthesis [21]. In fact, exposure of LNCaP cells to androgens caused a doubling of the phospholipid content of the cells [21].

Increased synthesis of fatty acids and cholesterol is governed by androgens through stimulation of the expression of whole sets of lipogenic enzymes, covering the entire pathways of fatty acid and cholesterol synthesis (Table 1) [20,22]. Androgen regulation of these genes (or of a more limited set of representative genes) has been found in all androgen-responsive prostate cancer cell lines tested (LNCaP, MDA-PCa2a, MDA-PCa-2b, PC-346c) [23] and has been confirmed by several independent DNA microarray studies [16,17]. Also in the androgen-responsive prostate cancer xenograft CWR22 [24] and in normal androgen-responsive tissues in vivo androgens stimulate lipogenic gene expression [25]. Along the same lines, in breast cancer cells, androgens as well as progestagens have been shown to potently activate lipogenesis and lipogenic gene expression [26,27]. In addition to these classical lipogenic genes several other genes involved in lipid binding, uptake, metabolism and transport have been shown to be androgen-regulated (Table 1).

3. Androgens stimulate lipogenesis through activation of the SREBP pathway

The finding that androgens enhance the expression of many genes involved in lipid metabolism points to a

Table 1
List of androgen-regulated genes involved in lipid metabolism

Gene	Function	Main reference
Fatty acid synthase (FAS)	Synthesis of fatty acids	[22]
Acetyl-CoA carboxylase (ACC)	Synthesis of fatty acids	[20]
Malic enzyme	Synthesis of fatty acids	[20]
ATP-citrate lyase	Synthesis of fatty acids	[20]
Stearoyl-CoA desaturase	Desaturation of fatty acids	[16]
Long-chain polyunsaturated fatty acid elongation enzyme 2 (HELO1)	Elongation of fatty acids	[16]
Long-chain fatty acid CoA ligase 3	Activation of fatty acids	[16]
Fatty acid amide hydrolase (FAAH)	Lipid signaling	[17]
Phosphatidic acid phosphatase type 2a	Lipid signaling	[28]
Acyl-CoA-binding protein	Transport of fatty acids	[16]
3-Hydroxy-3-methylglutaryl-CoA synthase	Synthesis of cholesterol	[20]
3-Hydroxy-3-methylglutaryl-CoA reductase	Synthesis of cholesterol	[20]
Farnesyl diphosphate synthase	Synthesis of cholesterol	[20]
3-β-Hydroxysterol-Δ-24 reductase (DHCR24)	Synthesis of cholesterol	[16]
Low density lipoprotein receptor (LDLR)	Uptake of cholesterol	[17]
SREBP-cleavage-activating protein (SCAP)	Cholesterol sensor and activator of lipogenesis	[23]
Sterol-regulatory element-binding protein-1c (SREBP-1c)	Lipogenic transcription factor	[20]
Sterol-regulatory element-binding protein-2 (SREBP-2)	Lipogenic transcription factor	[20]

coordinated regulation of clusters of genes constituting entire lipid metabolizing pathways. Key players in the regulation of lipid metabolism are the sterol regulatory element binding proteins (SREBPs) [29]. SREBPs are a family of three basic helix–loop–helix leucine zipper lipogenic transcription factors (SREBP-1a, SREBP-1c, SREBP-2) that are synthesized as inactive precursor proteins anchored to the membranes of the endoplasmic reticulum (ER) (Fig. 1). There they interact with an SREBP-cleavage-activating protein (SCAP), which is retained in the ER by Insig retention proteins (Fig. 1) [30,31]. The SCAP/SREBP/Insig complex is stabilized by cholesterol. When sterol levels are low, the SREBP–SCAP complex is released from the Insig retention protein and travels to the Golgi apparatus where an amino-terminal SREBP fragment is released by a two-step mechanism of regulated intramembrane proteolysis (Rip) [32]. This transcriptionally active fragment is translocated to the nucleus and depending on the SREBP isoform activates the transcription of multiple genes involved in the synthesis, binding, metabolism and uptake of fatty acids and cholesterol.

Several lines of evidence indicate that androgens activate the SREBP pathway and that the lipogenic effects of androgens are largely mediated by this activation. (1) Androgens stimulate the nuclear accumulation of mature SREBP [20]. (2) Androgen stimulation of key lipogenic genes (fatty acid synthase, HMG-CoA synthase) is abolished when the SREBP binding sites in the proximal promoter are deleted or mutated [20,23]. (3) Introduction of a dominant-negative SREBP strongly suppresses the lipogenic effects of androgens [20,23].

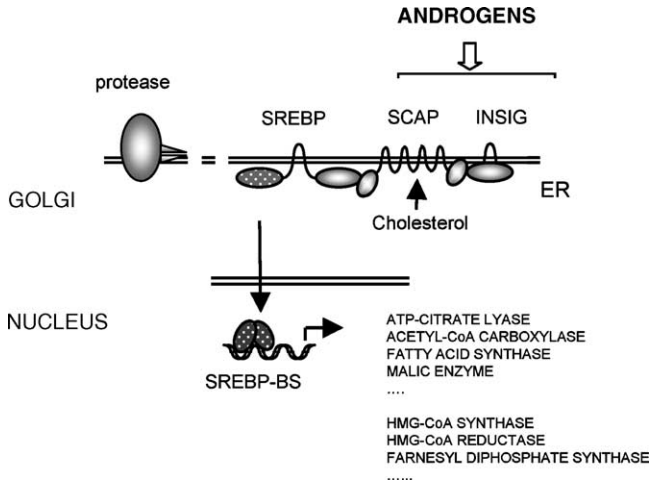

Fig. 1. Androgens stimulate lipogenic gene expression through interference with the mechanism governing cellular lipid homeostasis. Lipid homeostasis in mammalian cells is largely regulated by the SCAP/SREBP pathway. Sterol regulatory element-binding proteins are lipogenic transcription factors, synthesized as inactive precursors. SREBPs interact with SCAP, a SREBP cleavage-activating protein, which functions as a cholesterol sensor and which is retained in the endoplasmic reticulum (ER) by Insig retention proteins. Androgens stimulate the expression of SCAP and modulate the balance of SCAP and the Insig protein. Part of the SCAP pool is not retained by Insig and escorts the SREBP precursor to the Golgi, where a set of proteases cleaves the SREBP precursor. The amino-terminal fragment is released and is translocated to the nucleus where it binds to SREBP-binding sites (SREBP-BS) in numerous genes involved in lipid metabolism and activates their transcription.

Mounting evidence demonstrates that the primary sites of action of androgens on the SREBP pathway are SCAP and Insig retention proteins. Androgens markedly stimulate the expression of SCAP and cause a switch in the isoform expression of Insig ([23] and Heemers et al., unpublished data). This results in a change in the balance of the SREBP–SCAP complex on one hand and the retention protein complex on the other hand. The fraction of SCAP that is not retained by the retention protein would be free to escort the SREBP precursor to the Golgi apparatus leading to proteolytic maturation and activation of lipogenic gene expression. Androgens also stimulate the expression of SREBP-1c and SREBP-2 precursors, but these effects are thought to be secondary to the proteolytical activation of SREBPs. A similar mechanism of action as described for androgens has been proposed to explain the lipogenic effects of progestagens in adipocytes and in breast cancer cells [33]. These findings do not exclude additional direct effects of steroid hormones on individual genes allowing further fine-tuning of selected lipogenic processes. Moreover, in several instances the lipogenic effects of androgens are more pronounced than estimated from the changes in mRNA levels of lipogenic genes, suggesting that also translational and/or post-translational mechanisms are involved [21].

4. Lipogenesis in prostate cancer

In recent years, numerous reports have demonstrated overexpression of lipogenic enzymes such as fatty acid synthase and acetyl-CoA carboxylase, in a wide variety of cancer types including cancer of the breast, endometrium, ovaries, lungs, colon, oral cavity, several soft tissues, and the prostate, reviewed in [34]. In the prostate overexpression of fatty acid synthase has been studied most intensively and is found in the earliest stages of neoplastic transformation (PIN lesions) and in nearly all invasive carcinomas [35–37]. Intensity of immunohistochemical staining increased from low grade to high grade PIN and from low grade to high grade invasive carcinoma (Fig. 2) [35,36,38,39].

How and why lipogenic proteins are overexpressed in prostate cancer cells remains poorly understood. With respect to the mechanism underlying high level expression of fatty acid synthase, it is evident from the observations mentioned above that androgens and dysregulated androgen receptor function (resulting from mutations or from cross talk with other signaling pathways activated in malignant cells) play an important role. In LNCaP prostate cancer cells it has been shown that a mutation in the tumor suppressor gene encoding PTEN leads to constitutive Akt signaling and substantially contributes to the high level expression of fatty acid

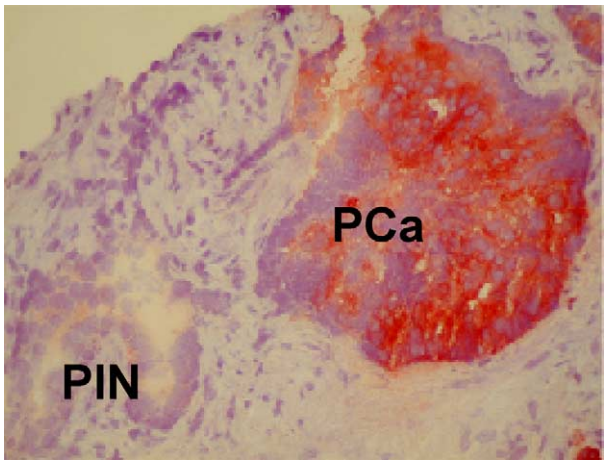

Fig. 2. Overexpression of fatty acid synthase in prostatic intraepithelial neoplasia (PIN) and in invasive carcinoma of the prostate (PCa). Immunohistochemistry was performed on cryostat sections of freshly frozen prostatic needle biopsies with a monoclonal antibody against fatty acid synthase [35]. The Envision technique (Dako) was used for visualisation. Cells were counterstained with Mayer's haemalum. Note the enhanced fatty acid synthase expression (red) in PIN and the very intense red staining in PCa.

synthase [40]. Exposure to growth factors such as epidermal growth factor (EGF) further enhances lipogenic enzyme expression in this cell line [41]. Similar to the lipogenic effects of androgens, growth factor-induced lipogenesis is in part governed at the transcriptional level and involves activation of SREBPs [41]. Similar mechanisms have been proposed in breast cancer cells [42,43]. In several instances the effects at the protein level are more pronounced than those at the transcriptional level, suggesting that translational and/or post-translational effects further enhance lipogenic enzyme expression and activity [36,40].

While the cancer-associated function of fatty acid synthase and of lipogenesis in general is just starting to be elucidated, it is clear that in most tumor cells examined the majority of newly synthesized lipids are phospholipids [37,44]. As phospholipids are the major building blocks of membranes it is tempting to speculate that increased lipogenesis in cancer cells reflects the high rate of membrane synthesis in rapidly dividing cells. In most clinical prostate cancers, however, only a fraction of the cancer cells are at one moment engaged in an active cell cycle, while nearly all cancer cells express high levels of fatty acid synthase [35]. Moreover, in contrast to the lipids derived from the diet which are relatively rich in polyunsaturated fatty acids, the newly synthesized phospholipids are enriched in saturated and in monounsaturated fatty acyl chains ([44] and unpublished data). Together with cholesterol these phospholipids tend to partition into detergent-resistant membrane microdomains [44–46]. These are raft-aggregates implicated in key cellular processes including intracellular trafficking, signal transduction and cell migration [47–50]. Hence, it is expected that increased lipogenesis in cancer cells affects multiple key aspects of tumor cell biology and actively contributes to the development and the progression of cancer.

5. Lipogenic genes as novel targets for antineoplastic therapy

One of the main obstacles in the management of prostate cancer is the treatment of metastatic disease. While androgen ablation initially produces favorable responses, it almost inevitably leads to transition of a lethal androgen-independent disease [10]. Interestingly, fatty acid synthase expression is highest in metastatic disease and while fatty acid synthase expression in prostate cancer is initially sensitive to androgens, this sensitivity is lost in parallel with the emergence of the androgen independent-phenotype [36,37]. In the CWR22 xenograft model of prostatic adenocarcinoma, fatty acid synthase expression drops after castration but re-emerges with the transition to androgen independence [24]. The sustained overexpression of fatty acid synthase through all stages of prostate cancer development and progression, renders fatty acid synthase (and several other lipogenic genes that are co-regulated) an interesting target for cancer prevention and for anticancer treatment.

Since the 1960's cerulenin (2*R*,3*S*)-2,3-epoxy-4-oxo-7,10-trans,trans-dodecadienamide), a natural antimetabolite

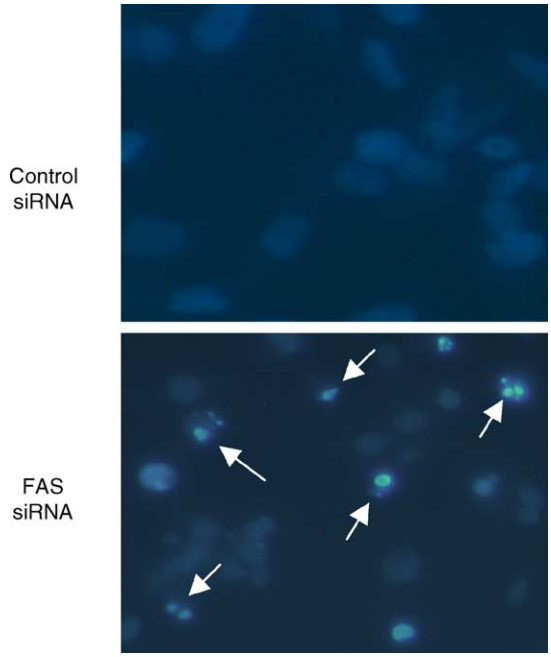

Fig. 3. Knock-down of fatty acid synthase (FAS) by RNA interference induces apoptosis in LNCaP prostate cancer cells. LNCaP cells were transfected with small interfering RNAs (siRNAs) targeting fatty acid synthase or with non-specific control siRNAs. At 72 h after transfection, cells were stained with Hoechst 33342 and analyzed by fluorescence microscopy. Note the apoptosis-associated chromatin condensation and nuclear fragmentation (arrows) after fatty acid synthase knock-down.

from the fungus *Cephalosporium caerulens* has been known as an inhibitor of fatty acid synthesis in several species. Cerulenin forms a covalent bond with the active site cysteine of the β-keto-acyl synthase subunit of fatty acid synthase and irreversibly inhibits its activity [51]. Treatment of human cancer cell lines including prostate cancer cell lines with cerulenin reduces cell proliferation and induces cell death [37,52,53]. Systemic treatment of nude mice bearing prostate cancer xenografts with the more stabile fatty acid synthesis inhibitor C75 significantly reduces tumor growth [37]. The selectivity and safety of these components, remains however a matter of debate [54]. Interestingly, recent evidence indicates that the major green tea polyphenol epigallocatecin gallate (EGCG), which largely mediates the cancer preventive effects of green tea, is a potent inhibitor of fatty acid synthase in prostate cancer cells [55]. The finding that treatment of cancer cells with small interfering RNAs targeting fatty acid synthase attenuates cancer cell proliferation and induces apoptosis, further underscores the potential of fatty acid synthase as an antineoplastic target and opens new avenues toward the development of more selective ways to interfere with tumor-associated lipogenesis (Fig. 3) [56].

6. Conclusions

Increased lipogenesis is an important hallmark of neoplastic cells and androgens are major regulators of this process in prostate cancer cells. Androgens stimulate lipogenesis largely through interference with the molecular mechanism controlling cellular lipid homeostasis. The resulting increase in the coordinate expression of multiple enzymes involved in the synthesis, metabolism and transport of fatty acids and cholesterol mainly serves the synthesis of phospholipids partitioning into membranes and more in particular into membrane microdomains. While increased lipogenesis is initially androgen-responsive it persists or re-emerges with the development of androgen-independent cancer, indicating that lipogenesis is a fundamental aspect of prostate cancer cell biology and is a potential target for chemoprevention and for anti-neoplastic therapy in advanced prostate cancer.

Acknowledgements

This work was supported by Cancer Research Grants from FB Insurance (Fortis Bank) and VIVA, by a grant ‘Geconcerteerde Onderzoeksactie van de Vlaamse Gemeenschap’, by research grants from the fund for Scientific Research, Flanders (Belgium) (F.W.O.), by a grant Interuniversity Poles of Attraction Programme, Belgian State, Prime Minister’s Office, Federal Office for Scientific, Technical and Cultural Affairs, and by a specialization grant from the Institute for the Enhancement of Innovation by Science and Technology in Flanders (IWT) (to H. Heemers). T. Van de Sande is a research assistant of the Fund for Scientific Research-Flanders (Belgium).

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