Androgen control of lipid metabolism in prostate cancer: novel insights and future applications

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Abstract

One of the most typical hallmarks of prostate cancer cells is their exquisite dependence on androgens, which is the basis of the widely applied androgen deprivation therapy. Among the variety of key cellular processes and functions that are regulated by androgens, lipid metabolism stands out by its complex regulation and its many intricate links with cancer cell biology. Here, we review our current knowledge on the links between androgens and lipid metabolism in prostate cancer, and highlight recent developments and insights into the links between key oncogenic stimuli and altered lipid synthesis and/or uptake that may hold significant potential for biomarker development and provide new vulnerabilities for therapeutic intervention.

Key Words
- lipid metabolism
- phospholipids
- androgens
- lipogenic enzymes
- prostate cancer
- lipidomics

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Androgens and prostate cancer

Prostate cancer is the most commonly diagnosed cancer, and the second leading cause of cancer-related death, in men in the developed world (Jemal *et al*. 2010). In 1941, Huggins and Hodges demonstrated that prostate epithelial cells are dependent on androgenic hormones for growth and survival. Accordingly, the primary treatment for men with metastatic prostate cancer for the past 70 years has been suppression of androgen production by surgical or medical castration, termed androgen deprivation therapy (ADT). While ADT is initially effective (reviewed in Klotz 2008), patients eventually relapse within 18–24 months; this incurable phase of the disease is called castrate-resistant prostate cancer (CRPC) (Asmane *et al*. 2011). Androgens mediate their actions through binding to the androgen receptor (AR), a ligand-dependent transcription factor and a member of the nuclear receptor superfamily. A plethora of adaptive mechanisms including AR amplification, mutation, and expression of splice variants has been demonstrated to maintain functional receptor signaling in CRPC (Scher *et al*. 2004, Knudsen & Scher 2009, Mills 2014), and consequently AR remains the primary therapeutic target for metastatic and advanced prostate cancer (Knudsen & Scher 2009). The development and FDA approval of agents that more effectively target AR signaling, including enzalutamide (Xtandi; an AR antagonist) and abiraterone acetate (Zytiga; an inhibitor of intratumoral androgen synthesis) (Tran *et al*. 2009, Cai & Balk 2011, Rodrigues *et al*. 2014), has expanded the therapeutic options for CRPC. Nevertheless, even these approaches cannot durably control tumor growth and there is considerable variability in the nature and duration of responses between different patients. Key to improving outcomes for patients with prostate cancer is a more detailed understanding of the key networks of cellular

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processes involved in tumor biology that are regulated by androgen action. This will not only reveal new approaches to suppress AR signaling, but also identify biomarkers that can more precisely indicate the optimal treatments for specific patients and monitor their responses.

Altered lipid metabolism is a hallmark of prostate cancer cells

One of the cellular processes most strikingly affected by androgens is lipid metabolism (Swinnen *et al*. 2006, Zadra *et al*. 2013). For many years, it has been noted by nuclear magnetic resonance spectroscopy that clinical prostate tumors, particularly more advanced and aggressive cases, often exhibit intense lipid signals, denoted as 'mobile lipids'. These mobile lipids largely correspond to phosphatidylcholine and particularly triglycerides and cholesterol esters found in cellular deposits now known as lipid droplets. Accumulation of lipid droplets has also been demonstrated by other methods including histological staining and Raman spectromicroscopy in more aggressive clinical prostate tumors and metastatic deposits (Yue *et al*. 2014), and in circulating prostate tumor cells (CTCs) (Mitra *et al*. 2012). While altered lipid metabolism is acknowledged as a hallmark of many cancers, until relatively recently, it was commonly regarded as an epiphenomenon that accompanied tumorigenesis. It is now appreciated that cancer cells have a markedly increased need for lipids, which serve as building blocks for membrane production, energy generation and storage, and intracellular signaling. This not only supports deregulated proliferation of cancer cells but also maintains their survival in a hostile microenvironment characterized by hypoxia and limited vascularity (Ackerman & Simon 2014).

While uptake of dietary lipids from the circulation is sufficient for the requirements of most normal cells, lipids are acquired by cancer cells in two main ways (Fig. 1). First, cancer cells overexpress enzymes in order to synthesize lipids *de novo,* and this cellular shift to *de novo* lipogenesis is associated with poorer prognosis for a wide range of tumor types, including prostate and breast cancers (Swinnen *et al*. 2006, Menendez & Lupu 2007). Activation of this pathway involves changes at all levels of lipid enzyme regulation (genetic changes, enhanced transcription and translation, protein stabilization and phosphorylation, allosteric regulation and substrate flux) and occurs downstream of various common oncogenic events, including loss of *PTEN*, activation of Akt, loss or mutation of *p53* or *BRCA1*, steroid hormone action, and tumor-associated hypoxia (Kuhajda 2006, Swinnen *et al*. 2006, Wang *et al*. 2013, Naguib *et al*. 2015, Rueda-Rincon

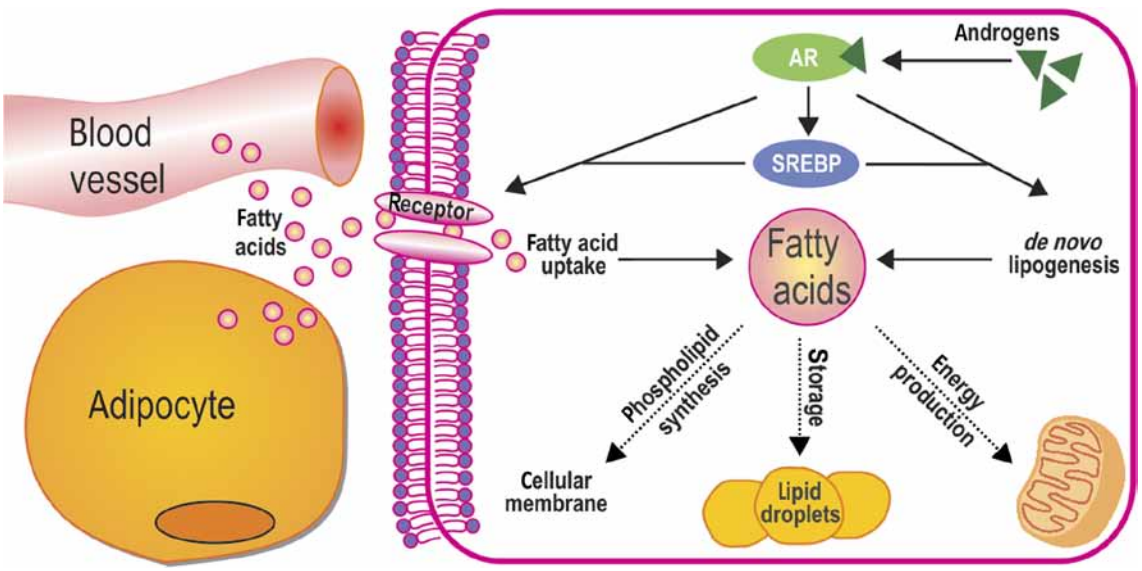

Figure 1
Androgens influence both synthesis and uptake of fatty acids in prostate cells. By activating SREBP1, the master regulator of lipid metabolism, androgens bound to the androgen receptor (AR) to stimulate the transcription of enzymes required for *de novo* lipogenesis and receptors that mediate the uptake of fatty acids released by lipolysis from the circulation and adipocytes. More recent evidence implicates direct activation of lipogenic gene transcription by AR signaling as an alternate mechanism by which androgens regulate fatty acid metabolism. Within the cell, fatty acids may then be oxidized for energy, stored as energy in lipid droplets, or converted to more complex phospholipids and incorporated into cellular membranes.

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et al. 2015). Secondly, cancer cells can take up exogenous lipids from the circulation and actively stimulate mobilization and release of stored lipids from intracellular lipid droplets or adipocytes in the tumor microenvironment, a process called lipolysis (Kuemmerle *et al*. 2011, Zaidi *et al*. 2013). Prostate cancer cells differ from many other cancer types, in that they predominantly utilize these fatty acids as energetic substrates, rather than glucose (Liu *et al*. 2010). This process is comparatively understudied in contrast to *de novo* lipogenesis; however, there is an increasing view that both are likely to be important sources of lipids to support prostate cancer cell proliferation (Zaidi *et al*. 2013).

Fatty acids that are synthesized or acquired by prostate cancer cells undergo catabolism via beta-oxidation for energy production (Carracedo *et al*. 2013), are stored in lipid droplets to protect them from harmful peroxidation (Bailey *et al*. 2015, Liu *et al*. 2015), or are ultimately converted to more complex phospholipids that are key components of cellular membranes (Fig. 1). Phospholipids are composed of a polar headgroup (e.g. choline, ethanolamine, serine, inositol) and fatty acyl chains that can differ both in length and the number of unsaturations (double bonds), leading to hundreds of different potential lipid species. Because mammalian cells lack the enzyme delta-12 desaturase to generate polyunsaturated acyl chains *de novo*, newly synthesized lipids are enriched in saturated and monounsaturated fatty acid chains. Consequently, enhanced lipogenesis not only helps meet the increased need of tumor cells for membranes to support rapid cell proliferation, it also enhances membrane phospholipid saturation (Rysman *et al*. 2010), which significantly affects numerous aspects of cancer cell biology. Functioning as barriers that separate and compartmentalize the cell's content, membranes play a central role in cell biology as unique interfaces at which numerous cellular processes (including signaling, nutrient transport, cell division, respiration, and cell death mechanisms) are concentrated and regulated. Membranes are also remarkably fluid structures, in which its constituent lipids readily diffuse throughout the plane of the bilayer, and this fluidity is regulated by the composition of phospholipids and cholesterol in the membrane. Fully saturated lipids pack densely into the plasma membrane, resulting in more rigid, impermeable membranes, and tend to partition into detergent-resistant membrane microdomains that are involved in the activation of oncogenic signaling pathways (Swinnen *et al*. 2003). Unsaturated lipids, on the other hand, pack less densely due to the presence of double bonds causing 'kinks' in the acyl chains, thereby enhancing membrane fluidity. As a result of *de novo* lipogenesis, membranes enriched for more saturated lipid species have altered polarity and loss of the cellular sensory cilia (Willemarck *et al*. 2010, Gijs *et al*. 2015), and are highly resistant to free radical damage, immune recognition, cell death, and chemotherapeutic insults (Rysman *et al*. 2010). Interestingly, recent evidence indicates that the synthesis of unsaturated lipids also plays a key role in cancer cell survival in response to hypoxia or oncogenic signals, by relieving endoplasmic reticulum stress (Young *et al*. 2013). In view of the emerging evidence that altered lipid metabolism affects numerous aspects of cancer cell biology, it is likely that changes in the composition of lipid species in a cell (i.e. the 'lipidome') serve to support the cancer phenotype (Santos & Schulze 2012).

Lipid metabolism is androgen-regulated in prostate cancer

In benign and malignant prostate cells, androgens have a marked stimulatory effect on multiple metabolic pathways, including lipid metabolism (Rysman *et al*. 2010, Barfeld *et al*. 2014). In the normal prostate, this anabolic action is essential to maintain the secretory function of the prostate gland required for optimal male fertility. In the case of tumor cells, we observed in 1996 that exposure of LNCaP prostate cells to natural or synthetic androgens leads to a marked accumulation of lipid droplets in the cytoplasm, largely via increased synthesis of fatty acids and cholesterol (Swinnen *et al*. 1996). Importantly, this lipogenesis was reversed by an AR antagonist and was not observed in AR-negative prostate cancer cells. Since that first key observation, androgens have been shown to stimulate expression of over 20 enzymes involved in lipid synthesis, binding, uptake, metabolism, and transport (Swinnen *et al*. 1997, Swinnen *et al*. 2004, Barfeld *et al*. 2014), thereby influencing the entire lipid profile of prostate cells in a coordinated manner.

Androgens stimulate lipid synthesis, uptake, and storage

De novo lipogenesis describes the conversion of acetyl-coenzyme A (acetyl-CoA, generated from citrate or acetate) to basic saturated fatty acids. The rate-limiting step in this process is the conversion of acetyl-CoA to malonyl-CoA, which is catalyzed by the enzyme acetyl-CoA carboxylase (ACC). Fatty acid synthase (FASN) then couples acetyl and malonyl groups to produce long-chain saturated fatty acids (mainly palmitic acid, C16:0), and

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stearoyl-CoA desaturase (SCD) converts saturated fatty acids such as palmitic acid to monounsaturated species. Elongases (ELOVLs), of which there are seven family members, catalyze the elongation of fatty acids, with different family members having different specificities for chain length and saturation level. It is well documented that the expression of each of these classes of enzymes, as well as those involved in cholesterol synthesis, is regulated by androgens (Swinnen *et al*. 1997, Gorlov *et al*. 2009, Massie *et al*. 2011, Sharma *et al*. 2013).

While most research attention has focused on the actions of androgens on *de novo* lipogenesis, AR signaling may also regulate cellular uptake of exogenous lipids by prostate cancer cells (Pinthus *et al*. 2007, Liu *et al*. 2010, Mitra *et al*. 2012, Sacca *et al*. 2012, Taylor *et al*. 2015). These lipids can be derived from dietary lipoproteins in the circulation, which are hydrolyzed by lipoprotein lipase to free fatty acids, or be released by lipolysis from stores in local adipose tissue depots that comprises a major component of the tumor microenvironment (Ribeiro *et al*. 2012). Androgens are generally viewed to stimulate lipolysis of fatty acids from adipocytes (O'Reilly *et al*. 2014), and have been reported to induce the expression of cell surface proteins that regulate the uptake of lipids from the extracellular microenvironment, including phosphatidic acid phosphatase type 2 (Ulrix *et al*. 1998) and plasma membrane fatty acid binding protein (Pinthus *et al*. 2007). Collectively, these actions of androgens could result in a vicious cycle of fatty acid release from the adipose-rich tumor microenvironment and enhanced uptake by the tumor cells. The volume and composition of the adipose tissue is altered by metabolic syndrome or obesity, which may in turn influence lipid availability and utilization. While there is conflicting data on the effect of obesity on the risk of developing prostate cancer, there is now strong evidence that obese men have more aggressive disease at diagnosis and a higher rate of recurrence following surgery (reviewed in Balaban *et al*. (2015), Taylor *et al*. (2015)). In cell line models, lipids taken up by prostate cancer cells can drive proliferation (Nieman *et al*. 2013) and potentially invasiveness (Sacca *et al*. 2012). Moreover, a recent report has demonstrated enhanced migration of prostate cancer cells induced by coculture with periprostatic-derived adipocytes from obese compared with lean mice (Laurent *et al*. 2016). Given that the antitumor effects of inhibiting lipogenesis can be overcome by providing exogenous fatty acids (Kuemmerle *et al*. 2011, Griffiths *et al*. 2013, Daniels *et al*. 2014), uptake of fatty acids by prostate tumor cells may be an important mechanism of clinical resistance to inhibitors of lipid synthesis (e.g. FASN inhibitors), particularly in a setting of obesity. Combining these agents with either AR-targeting strategies or lipid uptake inhibitors may be a useful strategy to limit acquisition of lipids by prostate cancer cells and achieve more durable patient responses.

Mechanisms of androgenic regulation of lipid metabolism

Currently, the best-characterized mechanism by which androgens may stimulate *de novo* lipogenesis and lipid uptake is through indirect activation of a family of transcription factors called sterol regulatory element-binding proteins (SREBPs) (Swinnen *et al*. 1997) (reviewed in Heemers *et al*. (2006)). SREBPs, comprising SREBP1a, 1c, and 2 isoforms, regulate the expression of most of the enzymes required for lipid synthesis and uptake, making them master regulators of lipid homeostasis in cells. In their inactive form, SREBPs are anchored to the endoplasmic reticulum membrane as part of a complex containing SCAP (SREBP cleavage activating protein) and INSIGs (insulin-induced genes-1 and -2) (Fig. 2). In response to decreased intracellular sterol levels, the interaction between SCAP and INSIG is lost and the SCAP–SREBP complex translocates to the Golgi, where it undergoes cleavage by site-1 and site-2 proteases. The resultant N-terminal domain of SREBP translocates into the nucleus, where it binds to specific sterol-response elements (SREs) to induce transcription of many of the key enzymes involved in *de novo* lipogenesis. Phosphorylation of SREBP by the energy sensor 5′AMP-activated kinase (AMPK) can prevent this proteolysis and nuclear translocation (Li *et al*. 2011). Inhibition of SREBP1 activity has been achieved by shRNA knockdown or the synthetic inhibitor fatostatin, and indirectly by activation of the energy sensor AMPK by agents such as silibilin. Each of these approaches result in repressed expression of key enzymes involved in lipogenesis, reduced cellular levels of fatty acids, and suppressed growth of tumor xenografts for a range of cultured prostate cell lines (AR-positive and AR-negative) (Huang *et al*. 2012, Li *et al*. 2014, Nambiar *et al*. 2014, Zadra *et al*. 2014, Nambiar *et al*. 2015). In the case of silibilin, these effects were restricted to tumor and not nonmalignant prostate cell lines (Nambiar *et al*. 2014). Collectively, this evidence supports a key role for SREBP-directed lipogenesis in supporting growth and survival of prostate tumor cells.

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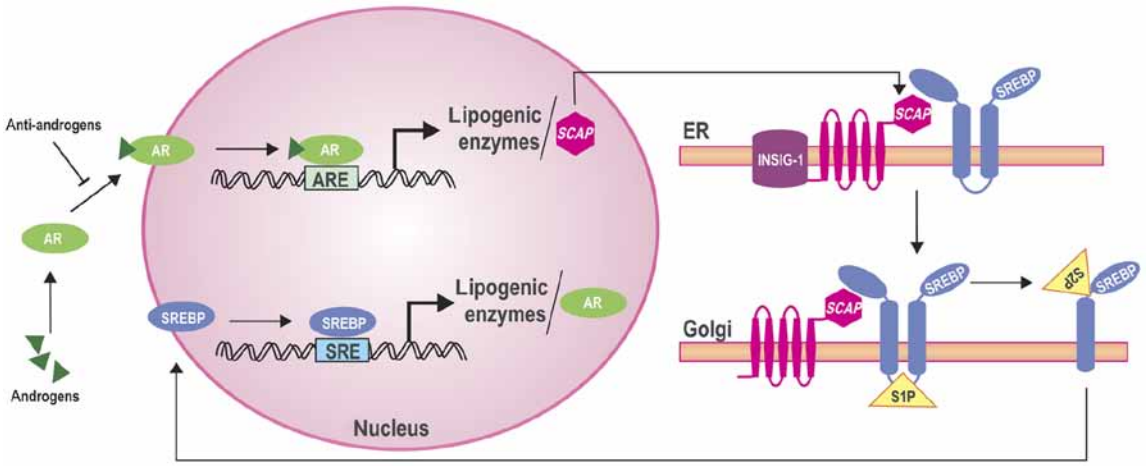

Figure 2
Mechanism of androgenic regulation of lipid metabolism. Androgens exert their effects by binding to the androgen receptor (AR), a ligand-activated transcription factor. While there is evidence that the AR can directly activate transcription of lipogenic enzymes, the best-characterized mechanism by which AR stimulates fatty acid metabolism is via activation of SREBPs. Direct induction of the SREBP cleavage-activating protein (*SCAP*) gene by AR facilitates translocation of SREBP1 to the Golgi for cleavage. The resultant activation of SREBP1 stimulates transcription of a large suite of genes required for lipogenesis and fatty acid uptake, including the AR itself.

The interactions between androgens and SREBPs are complex and remain incompletely understood. Androgens enhance both the expression and activation of SREBPs (Swinnen *et al*. 1997), although this is indirect, being mediated not by the transcriptional activity of the AR, but rather autoregulation of SREBP transcription as a result of activation via proteolytic cleavage of SREBP (Swinnen *et al*. 1997). More recent evidence indicates that this activation may be mediated via transcriptional induction of SCAP levels via binding of the AR to an ARE in the body of the *SCAP* gene (Fig. 2), thereby favoring translocation of SREBP precursors to the Golgi for cleavage (Heemers *et al*. 2004, Zhou *et al*. 2012). SREBPs can reciprocally activate the expression of AR via binding to an SRE in the 5′-untranslated region of the *AR* gene (Fig. 2) (Huang *et al*. 2010), and modulation of SREPB1 activity has parallel effects on AR expression and function (Fig. 2) (Huang *et al*. 2012, Li *et al*. 2014). Collectively, these mechanisms indicate that androgens can exert a coordinate and profound control over lipogenesis in both normal and neoplastic cell settings, and that normally this is tightly regulated by the reciprocal relationship between AR and SREBP activity.

Recent studies have provided new mechanistic insights into the link between SREBP, androgens, and uptake of extracellular lipids in prostate cancer cells. Investigators associated specific accumulation of esterified cholesterol within the lipid droplets of clinical prostate tumors, which was most pronounced in high-grade disease, with loss of *PTEN* and resultant activation of the PI3K/Akt pathway (Yue *et al*. 2014). Akt-mediated induction of SREBP in turn upregulated the expression of low-density lipoprotein (LDL) receptor on the cell surface, and enhanced the uptake of free cholesterol, which was then esterified and incorporated into lipid droplets. Interference with this pathway suppressed prostate cancer growth *in vitro* and *in vivo* and represents a promising therapeutic strategy. While this study did not find a direct relationship between androgen signaling and cholesterol uptake by the prostate cell lines, the protein Plk1, a mediator of oxidative stress in prostate cancer cells in response to stress stimuli such as androgen deprivation, has been implicated as a key upstream activator of the PI3K pathway (Zhang *et al*. 2014). PI3K/Akt signaling exhibits bidirectional crosstalk with AR signaling (Carver *et al*. 2011, Qi *et al*. 2015, Gao *et al*. 2016), providing a further level of complexity as both PI3K/Akt and AR lie upstream of SREBP activity and have the potential to either enhance or interfere with each other's ability to regulate lipogenesis and lipid uptake.

Recent genome-wide analyses of AR binding and activity have suggested a potentially distinct role for the AR in direct transcriptional regulation of lipogenic genes. Canonical AR action involves nuclear translocation of the ligand-bound receptor and binding as a dimer to specific DNA sequences found in AR binding sites (ARBs), often in the vicinity of androgen-regulated genes. This DNA binding precedes the recruitment of transcriptional machinery

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and coregulators, and results in altered gene transcription. Cistromic data of AR binding in chromatin of prostate cancer cells and clinical tumors have revealed that ARBs commonly occur in the vicinity (within 25 kb) of genes involved in general cellular and lipid metabolism (Barfeld *et al*. 2014). Based on their proximity to AR binding sites, and their transcriptional regulation by androgens, many genes involved in lipid metabolism (e.g. FASN, ACACA) and other key cellular metabolic processes have the potential to be directly regulated by the AR in both nonmalignant and malignant prostate cells (Massie *et al*. 2011, Sharma *et al*. 2013). This indicates that, in addition to their effects on SREBPs, androgens may also directly stimulate a coordinated metabolic network that enhances aerobic glycolysis and lipid biosynthesis, thereby supporting tumor cell growth and survival. Interestingly, inspection of the transcriptional data reveals marked variability in the extent and timecourse of transcriptional regulation between individual lipogenic genes by androgens, indicating that there is most likely a combination of direct and indirect mechanisms involved. Ablation of the putative ARBs in the vicinity of these genes will be essential to confirm direct regulation by androgens. The fact that targeting of many of these metabolic pathways has been the subject of intense investigation will underpin the design of rational combinatorial strategies to cotarget the AR and its metabolic target genes or pathways involved in lipid and general cellular metabolism.

Genes involved in lipid metabolism are altered in clinical prostate tumors

The clinical significance of the relationship between androgens and lipid metabolism is highlighted by reports that FASN, ELOVL7, and SREBP proteins are commonly overexpressed in human prostate tumors compared with normal or benign prostatic hypertrophic tissue (Swinnen *et al*. 2002, Rossi *et al*. 2003, Ettinger *et al*. 2004, Tamura *et al*. 2009), with the expression of SREBP1 in particular showing positive associations with disease progression and Gleason grade (Ettinger *et al*. 2004, Huang *et al*. 2012). Consistent with their androgenic regulation, both FASN and SREBP levels are initially decreased in patients treated with ADT but re-emerge with a higher level of expression in CRPC (Rossi *et al*. 2003, Ettinger *et al*. 2004). Moreover, interrogation of publicly available mRNA datasets has revealed significant increases in the expression of SREBP and multiple androgen-regulated genes involved in lipid metabolism and beta-oxidation in prostate tumors compared with nonmalignant prostate (Wu *et al*. 2014).

In light of these observations, targeting the metabolic and lipidomic features of tumor cells is a rational therapeutic strategy, and is the subject of several recent excellent reviews (Fritz *et al*. 2013, Comerford *et al*. 2014). FASN in particular has received considerable attention as a potential therapeutic target (Mullen & Yet 2015) and small molecule inhibitors of FASN, including the antiobesity agent orlistat, have demonstrated promising preclinical efficacy in prostate tumor models (reviewed in Menendez & Lupu (2007), Zadra *et al*. (2013), Wu *et al*. (2014)). Unfortunately, despite active drug discovery efforts, the clinical translation of these agents to date has been limited by unacceptable toxicity profiles (Mullen & Yet 2015).

Lipidomics: the understudied 'omic'

The fundamental role of androgens in regulating lipid metabolism has fuelled interest in studying the composition of lipids (i.e. the lipidome) in prostate tumors as a novel source of biomarkers of disease aggressiveness and response to AR-directed therapies. In contrast to the genome, transcriptome, or proteome, the lipidome and particularly the phospholipidome remain poorly explored as sources of biological information on the status or behavior of a cell. This is partly due to the requirement for state-of-the-art instrumentation and expertise to accurately and simultaneously measure the thousands of different lipid species present within a cell or tissue (Wenk 2010, Checa *et al*. 2015). However, recent developments in mass spectrometry methodologies and efforts to define phospholipid profiles in blood, cancer cells, and tissues have enabled the documentation of recurrent changes in prostate cancer cells compared with nonmalignant cells, and have facilitated the identification of specific lipid classes that are qualitatively and quantitatively altered in more aggressive metastatic cells (Rysman *et al*. 2010, Burch *et al*. 2015, Goto *et al*. 2015, Duscharla *et al*. 2016). MALDI (mass spectrometry imaging), Raman spectroscopy, and development of molecular probes directed to specific lipids afford novel opportunities to investigate not only the quantity but also the spatial distribution of specific lipids within a cell or tissue. Such analyses are instrumental for the identification of novel key changes in lipid metabolic pathways in cancer and hold great potential for lipid-based biomarker discovery and applications, including smart knife technologies. Moreover, as changes in lipid profiles can be measured in body fluids, and potentially visualized in tumors by molecular imaging, there is a high potential for the development of specific and minimally invasive tests. Most recently, advances are being made in

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the integration of lipidomic data with other 'omics' such as transcriptomics (Li *et al*. 2016). While challenging, this integration offers the exciting potential to use data-driven system approaches to identify key drivers of metabolic alterations, which may represent previously unrecognized therapeutic or preventative targets. Nevertheless, it remains impossible to measure the entire lipidome simultaneously using a single assay system, and the ability to feasibly perform targeted and quantitative lipidomic analysis in a healthcare setting will be essential to the future adoption of lipid-based biomarkers for disease prognostication, drug development, and treatment response (Zhang & Wakelam 2014, Dehairs *et al*. 2015, Hyotylainen & Oresic 2015).

Summary and perspective

Despite being markedly altered in prostate cancer, exquisitely sensitive to androgen hormones, and tightly linked to cancer cell biology, the potential of lipid metabolism to provide new information about the clinical behavior of prostate cancer and new targets for therapeutic intervention has not yet been fully realized. The intimate links between androgen signaling, oncogenic pathways, and lipid metabolism in prostate cancer cells make the prostate cancer lipidome a potentially unique indicator of tumor behavior and aggressiveness, and a source of novel therapeutic targets. Moreover, as current treatments for high-risk or advanced prostate cancer are specific inhibitors of androgen production or androgen binding to the AR, they would be expected to markedly alter the expression of enzymes involved in lipid metabolism in prostate cancer cells. In view of the dramatic changes in lipid metabolism evoked by androgens, lipidomics may be particularly advantageous as a means of monitoring the response of clinical prostate tumors to these antiandrogen therapies or progression to a castrate-resistant state. As expertise in lipid analysis becomes more widespread, and technologies improve in sensitivity and resolution, lipidomics will likely join metabolomics as complex and informative readouts of tumor biology, metabolism, and biomarker discovery.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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