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Review

# The fat side of prostate cancer[☆]

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ABSTRACT

Prostate cancer (PCa) metabolism appears to be unique in comparison with other types of solid cancers. Normal prostate cells mainly rely on glucose oxidation to provide precursors for the synthesis and secretion of citrate, resulting in an incomplete Krebs cycle and minimal oxidative phosphorylation for energy production. In contrast, during transformation, PCa cells no longer secrete citrate and they reactivate the Krebs cycle as energy source. Moreover, primary PCas do not show increased aerobic glycolysis and therefore they are not efficiently detectable with $^{18}$F-FDG-PET. However, increased de novo lipid synthesis, strictly intertwined with deregulation in classical oncogenes and oncosuppressors, is an early event of the disease. Up-regulation and increased activity of lipogenic enzymes (including fatty acid synthase and choline kinase) occurs throughout PCa carcinogenesis and correlates with worse prognosis and poor survival. Thus, lipid precursors such as acetate and choline have been successfully used as alternative tracers for PET imaging. Lipid synthesis intermediates and FA catabolism also emerged as important players in PCa maintenance. Finally, epidemiologic studies suggested that systemic metabolic disorders including obesity, metabolic syndrome, and diabetes as well as hypercaloric and fat-rich diets might increase the risk of PCa. However, how metabolic disorders contribute to PCa development and whether dietary lipids and de novo lipids synthesized intra-tumor are differentially metabolized still remains unclear. In this review, we examine the switch in lipid metabolism supporting the development and progression of PCa and we discuss how we can exploit its lipogenic nature for therapeutic and diagnostic purposes. This article is part of a Special Issue entitled Lipid Metabolism in Cancer.

## 1. Introduction

Prostate cancer (PCa) is the most commonly diagnosed malignancy in men and the second leading cause of cancer-related deaths in the USA [1]. Although the advent of PSA screening has led to an increase in the number of diagnoses for early intervention, PSA testing does not appear to decrease PCa mortality and some patients still experience disease progression after receiving primary treatment [2]. Currently, the standard systemic treatment for advanced PCa is based on androgen deprivation (LHRH agonists, often in combination with oral anti-androgens) to which tumors initially respond but eventually become castrate resistant by acquiring changes that include androgen-receptor overexpression and up-regulation of enzymes involved in androgen biosynthesis, which result in reactivation of the receptor. Based on the new understanding of these resistance mechanisms and androgen biosynthesis pathways, new anti-androgens and androgen-depleting agents have been developed (including enzalutamide and abiraterone acetate), hopefully increasing efficacy in advanced cancers [3]. Men with metastatic castration-resistant PCa (CRPC) have a median survival of less than 2 years [4]. Currently, there is no standard therapeutic modality for this fatal stage of PCa. Broad-band chemotherapeutic drugs are commonly used as a last resort; the taxane-derivative docetaxel is the only US Food and Drug administration (FDA)-approved treatment for use, showing a survival benefit, although several others are approved for palliative indications [5,6]. Unfortunately, tumors often develop resistance to taxanes [6]. Thus, alternative therapeutic strategies are urgently sought.

In the 1920s, the German biochemist Otto Warburg made the first observation that cancer cells undergo a metabolic reprogramming by increasing the uptake of glucose and converting it to lactate using glycolysis, even in the presence of normoxic conditions (a phenomenon called Warburg effect or aerobic glycolysis) [7]. Despite being a less efficient mechanism of ATP production, aerobic glycolysis proved to be the core cellular metabolism to provide cancer cells with building blocks for macromolecule synthesis, such as carbohydrates, proteins, lipids, and nucleic acids to support their accelerated proliferative rate [8].

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After one century, the importance of metabolic reprogramming in cancer has been re-discovered and in the last decade the use of new molecular tools allowed unraveling the numerous connections between oncogenic pathways and metabolic activities. Indeed, the identification of metabolic weaknesses of cancer cells has led to new strategies for treating cancer. PCa presents very unique metabolic features, since primary tumors do not show the classical "glycolytic switch" as the majority of other solid tumors, and so are not efficiently detectable with FDG-PET, a technique successfully used in oncology for non-invasive diagnosis, staging and treatment follow-up. However, an aberrant increase in de novo lipogenesis, directly coupled with glucose and glutamine metabolisms, is observed at early stages of the disease, significantly associated with tumor progression, worse prognosis, and shorter survival [9–12]. Moreover, lipid deregulation, due to systemic metabolic diseases (including obesity, metabolic syndrome, diabetes) or specific diet behaviors has been linked to an increased risk of prostate cancer, but the mechanism for this relationship is still not fully understood [13]. Although the production of amino acids and nucleic acids is certainly an integral characteristic of the cancer anabolic reprogramming as well, here, we discuss the alterations of lipid metabolism in PCa, how oncogenic signaling, diet, and lifestyle regulate it, and finally how we can take advantage of this understanding to develop novel diagnostic tools and therapeutic strategies.

## 2. Role of lipids in cancer

Lipids contribute to several aspects of tumor biology due to the diversity of their biological roles (Fig. 1). First, they function as building blocks for biological membranes to support the high proliferative rate of cancer cells. Several endogenously synthesized fatty acids (FAs) are esterified to phospholipids, which provide pivotal structural lipids, facilitate the formation of detergent-resistant membrane microdomains for signal transduction, intracellular trafficking, polarization, and migration required for cancer cells [9,14]. The importance of membrane synthesis in cancer cells has been underscored by the observation that the expression and activity of choline kinase, an enzyme required for the synthesis of phosphatidylcholine and phosphatidylethanolamine (the major phospholipids found in cellular membranes) is increased in tumors from several tissues, including PCa, and correlates with poor prognosis [15,16]. Choline kinase has oncogenic activity when overexpressed, suggesting that the synthesis of phospholipids is rate limiting for transformation [17,18].

Second, intermediates of de novo lipogenesis, such as diacylglycerol (DAG), phosphatidic acid (PA), lysophosphatidic acid (LPA), and sphingosine 1-phosphate (S1P) also function as second messengers in signal transduction pathways and are involved in crucial aspects of cell to cell communication. Once generated, these lipids can be released and act extracellularly in an autocrine/paracrine manner, controlling a variety of cellular functions such as cell proliferation, survival, and migration/invasion by either activating other signaling proteins, or by engaging a series of G protein-coupled receptors (GPCRs) on the cell surfaces [19]. Third, lipid-mediated post-translational modification of proteins is also a vital process in regulating expression, localization and function of various signaling proteins [20,21]. Phosphatidylinositol (PI)-associated modification through a carbohydrate linker to the proteins (GPI-anchored proteins) directs them towards the cell surface from the endoplasmic reticulum (ER) [22]. Some GPI-anchored proteins, such as urokinase-type plasminogen activator (uPA)-receptor (uPAR) and membrane anchored serine protease matriptase (also known as MT-SP1 and epithin), have a strong association with cancer [23,24]. Covalent attachment of FA palmitic acid to a serine residue (also called palmitoylation) of Wnt, an important signal molecule, regulates its signaling capacity and secretion [25,26]. Cytoplasmic stabilization of β-catenin through palmitoylation of Wnt-1 and subsequent activation of the pathway has been shown as a potential mechanism of fatty acid synthase (FASN)-mediated oncogenicity in PCa [27]. Moreover, the irreversible attachment of a myristoyl group (derived from FA myristic acid) to the N-terminal amino acid of Akt has been shown to activate the kinase and to induce cell transformation [28,29]. Prenylation (the transfer of either a farnesyl or a geranyl–geranyl moiety to C-terminal cysteine(s) of the target protein) is also involved in the regulation of signaling outputs and controls the trafficking of proteins among ER, Golgi and plasma membranes, including the Ras small GTPase family members [30]. Finally, in response to glucose limitation, FAs can also be consumed through β-oxidation to provide key substitute energy for cancer cell survival. It is reported that increased FA oxidation is sufficient for cell survival and to protect cells from glucose withdrawal-induced death in Akt-overexpressing glioblastoma [31]. In PCa, FA oxidation has been observed to be a dominant bioenergetic pathway, as discussed below [32].

## 3. Alteration of lipid metabolism in prostate cancer

### 3.1. Dysregulation of FA biosynthesis and its pleiotropic role in cancer cells

Altered lipid metabolism has been increasingly recognized as a classical hallmark of cancer cells and a growing body of literature has been focused on the relationship between up-regulated lipogenesis (the so called "lipogenic phenotype") and PCa pathogenesis [10,11,27,33,34]. A number of lipogenic enzymes utilize reduced nicotinamide adenine dinucleotide phosphate (NADPH) and acetyl-CoA generated from glucose and glutamine oxidation to synthesize FAs and their derivatives (Fig. 2). Therefore, the exacerbated lipogenesis in cancer cells is not only caused by the up-regulation of lipid metabolizing enzymes, but is also directly coupled to other common metabolic pathways and associated cell signaling pathways. FA synthesis occurs in the cytosol and begins with the conversion of citrate [derived from the tricarboxylic acid (TCA) cycle in the mitochondria] to acetyl-CoA and oxaloacetate by the enzyme ATP citrate lyase (ACLY). Acetyl-CoA is then converted to malonyl-CoA by the rate-limiting enzyme acetyl-CoA carboxylase (ACACA, commonly referred to as ACC), whereas oxaloacetate can be converted into pyruvate by the malic enzyme. This reaction generates NADPH and, along with the NADPH-producing reactions in the pentose phosphate pathway, provides the reducing power for lipid synthesis. The multi-enzymatic complex FASN then processes one acetyl-CoA and seven malonyl-CoA molecules through a series of catalytic domains to produce palmitate (16:0), a saturated 16-carbon FA that represents about 80–90% of total FAs produced in a cell, and the less abundant FAs myristate (14:0) and stearate (18:0) [9]. Saturated FAs may then undergo further modifications at the cytoplasmatic face of the ER membrane by desaturases and/or elongases to insert double bonds or increase the carbon chain length, respectively, before FAs are ultimately utilized for energy, protein modification, or incorporation into complex lipid structures for cellular signaling and membrane integrity [35] (Fig. 2). Desaturation is catalyzed by fatty acyl-CoA desaturases, including the family of stearoyl-CoA desaturases (SCDs) also known as fatty acyl-CoA delta-9 desaturases, that catalyze the introduction of the first double bond in the cis-delta-9 position of several saturated fatty acyl-CoAs, principally palmitoyl-CoA and stearoyl-CoA, to yield palmitoleoyl (16:1)- and oleoyl-CoA (18:1), respectively [36]. The best-characterized desaturase is SCD1, which is highly expressed in oncogene-transformed lung fibroblasts and in several cancers [37–40]. Recently, SCD1 has been found overexpressed both at the mRNA and protein level in androgen-sensitive and resistant PCa cell lines as well as human tumor tissues. In the latter, its overexpression correlates with a higher gleason grade, suggesting a role of this desaturase in PCa progression [41]. Elongation of FAs to produce FAs with longer chains such as stearic acid is obtained by a family of elongases that add two carbons to the end of the chain in each cycle of reactions. This family comprises seven members (ELOVL1-7) with different chain lengths and saturation specificity. Tamura and coworkers have recently shown that ELOVL7 is overexpressed in PCa and is involved