The Role of Sex Steroid Receptors on Lipogenesis in Breast and Prostate Carcinogenesis: A Viewpoint

Henri Rochefort · Dany Chalbos

Abstract Cancer cells require both nutrients and mitogens to multiply and survive in the unfavorable microenvironment of solid tumors or metastases before angiogenesis. Most cancer cells do not use fatty acids (FA) from the circulation but synthesize them in situ especially to make membranes and lipid signals required for continuously dividing cells. Three lipogenic enzymes are overexpressed, induced by sex steroid hormones and responsible for the in situ increased lipogenesis in cancer cells. We propose that in the early stages of human breast and prostate carcinogenesis, an increased activity of sex steroid receptors is partly responsible for the overexpression of FA synthase (FASN) whose regulation in cancer cells has been particularly studied. Increased activity of androgen receptor (AR), via different mechanisms, was extensively reported in prostate cancer. An increased level/and or activity of progesterone receptors, correlated with an increased expression of FASN, was found both in early stages of breast carcinogenesis and during the hormone replacement therapy of menopausal women. While the majority of recent targeted therapies are based on inhibition of mitogenic pathways, the inhibition of cancer cell nutrition by interfering with lipid synthesis and hormone action should open the way to new therapeutic and preventive approaches of hormone-dependent cancers.

Keywords Progestins · Androgens · Fatty acid synthase · Breast and prostate carcinogenesis

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Introduction

Most targeted cancer therapies are based on drugs that regulate transduction mechanisms and are directed against membrane or nuclear receptors. However, to form a colony that will survive and develop into a tumor or a metastasis in a foreign microenvironment under stringent conditions, cancer cells need not only to migrate and to enter an active G1 phase of the cell cycle but also need nutriments to grow. Indeed, carcinogenesis implies not only deregulation of signal transduction pathways that control the cell cycle leading to an anarchic DNA replication but also a concerted activation of cellular mechanisms enabling the production of a sufficient amount of proteins, lipids, and energy to allow cells to survive and grow in a hostile environment inside a solid tumor characterized by a high pressure, hypoxia, acidic pH, and poor vascularisation.

In hormone-dependent cancers, nuclear receptors (NR) activated by sex steroid hormones together with a large number of co-modulators, play a major role in the complex tissue-specific network induced by hormones during carcinogenesis to regulate cell proliferation and nutrition [1]. This overview is focused on lipogenic enzymes which are overexpressed in breast and prostate cancer cells and regulated by sex steroids. Unraveling the mechanism of this overexpression might help to understand not only the central role of androgens and their receptors in prostate

carcinogenesis but also the deleterious effect of progestins on breast cancer incidence in women treated with hormone replacement therapy (HRT) [2].

Increased In Situ Lipogenesis in Cancer Cells Compared to Normal Cells

In several solid tumors, including breast, prostate, lung, and colon carcinomas, cancer cells, due to their high requirement in energy and cell membrane, synthesize high amount of fatty acids (FA) via an increased expression and activity of lipogenic enzymes [3–5]. Figure 1 shows schematically the pathways leading to energy production and lipid synthesis in cancer cells. In many solid tumors, energy is mostly provided by high aerobic glycolysis with increased
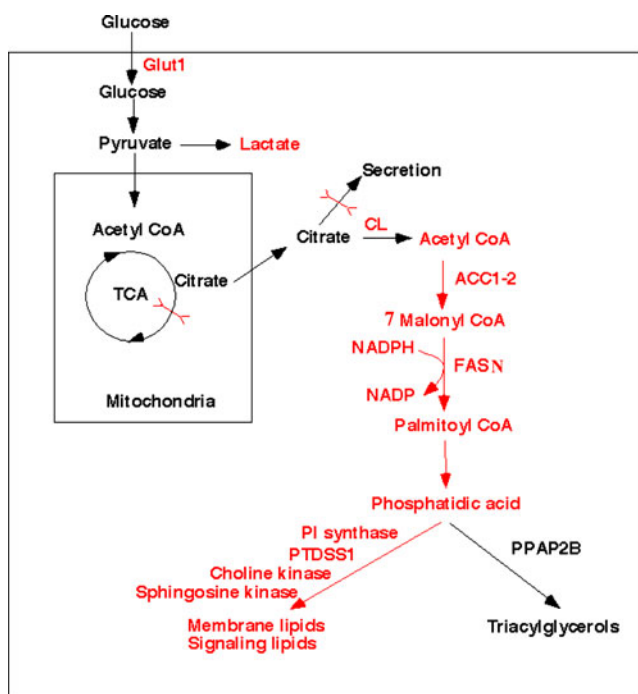
Fig. 1 Lipogenic phenotype of cancer cells. In situ lipogenesis in cancer cells (red) compared to normal cells (black) is characterized by an increased in situ synthesis of long chain fatty acids (palmitoyl CoA) due to the overexpression of three enzymes: ATP citrate lyase, (CL), acetyl-CoA carboxylase (ACC1/2), and fatty acid synthase (FASN). This pathway is upregulated by sex steroid hormones. The neosynthesized fatty acids are mostly used to make membrane phospholipids rather than to accumulate in triglycerides, the phosphatidic acid phosphatase (PPAP2B) expression being reduced (L. Fajas, unpublished data). The other enzymes involved in the synthesis of membrane and signaling phospholipids from phosphatidic acid, such as phosphatidyl inositol synthase (PI synthase), phosphatidyl serine synthase (PTDSS1), choline kinase, and sphingosine kinase, are also overexpressed but will not be considered here. In addition, energy is provided by the increased aerobic glycolysis (Warburg effect) with higher cellular uptake of glucose via the glucose transporter 1 (Glut 1). This results in more lactic acid and citrate production and less energy from the tricarboxylic Krebs cycle.

glucose uptake to the detriment of the Krebs tricarboxylic acid cycle in mitochondria. This Warburg effect leads to lactic acid secretion and decreased extra cellular pH, even in the presence of oxygen, and confer a selective growth advantage to cancer cells [5, 6]. The in situ biosynthesis of palmitic acid from citrate was demonstrated by different groups to be increased by sex steroid hormones in breast and prostate cancers for the synthesis of membrane and signaling phospholipids. Three enzymes involved in the synthesis of long-chain FA are overexpressed in breast and prostate cancers [3]. They are ATP citrate lyase, acetyl-CoA carboxylase (ACC1/2), a rate-limiting enzyme which generates malonyl CoA, and fatty acid synthase (FASN), the key multifunctional enzyme catalyzing the synthesis of long-chain FA from the condensation of acetyl CoA with malonyl CoA [7]. Several other enzymes involved in membrane lipid metabolism are also overexpressed. Some of them are important in oncogenesis, but will not be considered here since their hormonal regulation was less studied.

In normal nutritional conditions, FAs are provided by nutriments from lipid digestion. The lipogenic enzyme FASN is mostly expressed by liver, adipocytes, and lactating mammary gland but not in resting mammary gland and in normal prostate. FASN is induced by glucose, insulin, and T3 and rapidly downregulated by circulating FAs from the alimentary lipids to produce a suitable amount of FAs [5, 8, 9]. In contrast, in cancer cells, FASN expression appears to be insensitive to the downregulation by circulating FAs [9–11].

Several mechanisms can explain the FASN overexpression in most solid tumors. These mechanisms are not exclusive and may vary according to the type of cancer. The loss of the downregulation of FASN by circulating FAs may be explained by the fact that in vivo, circulating FA cannot reach cancer cells isolated from the circulation when they proliferate inside the basement membrane, like in breast carcinoma in situ (DCIS) and prostatic intraepithelial neoplasia (PIN). Hypoxia associated to the increased expression and activity of the hypoxia-induced transcription factor 1 (HIF1) is certainly one mechanism to consider to explain FASN overexpression. In most solid tumors, aerobic glycolysis (the "Warburg effect") [6] is often associated with higher FA synthesis. HIF1, via activation of Akt, induces SREBP-1 which stimulates expression of lipogenic enzymes including FASN [12, 13]. Gene amplification of the Spot 14 gene described in some lipogenic breast cancer [14] is associated with FASN overexpression. The overexpression or activity of acetyl-CoA carboxylase via single nucleotide polymorphisms of its gene was shown to be associated with an increased risk of breast cancer [15]. Moreover, the acetyl-CoA carboxylase protein is normally inhibited by its interaction with wild-type BRCA1, but not by the mutated inactive BRCA1, explaining an increased lipogenesis in these familial breast cancers [16]. However, for most of the

"sporadic" breast and prostate cancers, we propose that additional major mechanisms involve a deregulation by hormones in hormone-responsive cancers and by oncoproteins in hormone-resistant cancers.

Regulation of Fatty Acid Synthase by Sex Steroid Hormones in Breast and Prostate Cancers

The first data on the dysregulation of FASN expression have been obtained independently with progesterone in breast cancer and with androgens in prostate cancer.

Progestins Increase FASN Expression in Breast Cancer

In progesterone receptor (PR)-positive human breast cancer cell lines, Chalbos et al. [17, 18] reported that progestins induced an abundant 250-kDa cytoplasmic protein which was then identified as FASN. FASN mRNA induction by progestins was rapid (within 20 min), transcriptional, and not prevented by cycloheximide [19]. This suggested that the regulation was direct on FASN gene via a progesterone response element (PRE) described in the first intron in rat [20] or by the recruitment of PR by Sp1 bound on Sp1 sites of the 5′end of the FASN gene [21]. Progestins increased also FASN mRNA stability [19]. FASN was mostly regulated by progestins. The "pure" progestin R5020 and medroxy progesterone acetate (MPA), which also binds to the glucocorticoid receptor and androgen receptor (AR), were more active than progesterone which is metabolized in these cells [18]. Androgens were only active at micromolar concentrations; estrogens and glucocorticoids were inactive. However, in the absence of steroids, the growth factors EGF and IGF-1 and the growth factor receptor HER-2/Neu also increased FASN expression by stimulating the PI-3 kinase and MAP kinase pathways, leading to the cascade induction of the transcription factor SREBP1 and of FASN [22]. These pathways became predominant in tumor progression to hormone independency. In vivo, the same progestin induction of FASN was observed in estrogen receptor α (ERα) and PR-positive breast cancers. By in situ hybridization [23] and immunohistochemistry, FASN level was found to be maximal during the luteal phase of menstrual cycle in normal mammary glands [24] and endometrium [25]. The weaker effect of progesterone compared to the synthetic progestin MPA on FASN induction is probably due to its higher metabolism, which might also explain the lower deleterious effect on breast cancer risk of micronized progesterone compared to MPA in a cohort of postmenopausal women [26]. FASN overexpression in both ER-positive and ER-negative invasive breast cancers was found independently to be associated with an increased risk of recurrence and metastasis [27, 28].

Androgens Increase Lipogenesis in Prostate Cancer

The complex mechanism by which androgens induce FASN and acetyl-CoA carboxylase in prostate cancer has been fully investigated by the group of Swinnen and will not be detailed here. In this case, the upregulation appears to be mostly indirect via the transcriptional induction of the sterol regulatory element binding protein (SREBP) precursor mRNA [4, 29], the maturation of its precursor protein by a site 1 protease, and the stabilization of the FASN protein by the isopeptidase USP2a [29, 30].

Conversely, the Activation of Two Other Members of the NR Superfamily, the Peroxisome Proliferator-Activated Receptor Gamma (PPARγ) and Vitamin D3 Receptor, can Decrease FASN Expression, this Effect Being Mostly Described in Prostate Cancer Cells

Their eventual protective effect on carcinogenesis in facilitating cancer cell differentiation involves also other major mechanisms, not developed here since it is beyond the scope of this review.

Several mechanisms have been proposed to explain the decreased expression of FASN by ligands of these other nuclear receptors [31–33]. PPARγ ligands, such as the antidiabetic drug Troglitazone [32] or high doses of genistein which activates preferably the estrogen receptor β (see "Action Via Other Nuclear Receptors"), inhibit androgen action by decreasing AR transcriptional activity rather than AR expression level. Calcitriol by activating vitamin D3 receptor inhibits also FASN expression [33]. This inhibition occurred within 6 h of treatment of LNCaP cells, but was indirect since prevented by cycloheximide treatment. Androgens were required to observe the inhibition, suggesting that calcitriol was acting as an anti-androgen.

In Vivo, We Propose that an Increased Activity of PR in Breast Cancer and of AR in Prostate Cancer are at Least Partly Responsible for FASN Overexpression in the Early Steps of Carcinogenesis

In normal target tissues, FASN can be regulated by the same steroid hormones as in cancer. This was shown both for progestins in the human breast and endometrium [25, 26] and for androgens in rat ventral prostate [34]. However, in hormone-dependent cancers, the degree of this hormonal regulation appears to be more important and to bypass the normal physiological regulation by nutriments. We propose that this is partly due to an increased activity of the corresponding receptors. This proposal is based on much more data for androgens in human prostate cancer than for progesterone in breast cancer (Fig. 2).
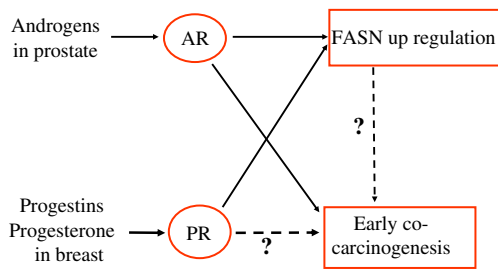
Fig. 2 Schematic representation of our view on the role of two sex steroid receptors on FASN synthesis and in prostate and breast carcinogenesis: Androgens via AR in prostate and progestins via PR in breast are clearly involved in inducing FASN expression ("Regulation of Fatty Acid Synthase by Sex Hormones in Breast and Prostate Cancers"). The role of androgens and its receptor activation as tumor promoter agents in prostate cancer is extensively documented. The role and mechanism of action of progesterone, synthetic progestins, and their receptors in facilitating breast carcinogenesis are more debated due also to the heterogeneity of breast cancers. We propose that an increased activity of these two sex steroid receptors is partly responsible for the FASN overexpression which then contributes to facilitate the early steps of carcinogenesis.

AR in Prostate Cancer

Most studies have found an increased level or activity of AR in prostate cancer cells associated to an increased expression of AR-regulated genes, such as *FASN* and *PSA* (reviewed in [34]). Whatever is their mechanism, the FASN overexpression and the increased level or activity of AR appear to be general and early events in carcinogenesis since these are already observed in most of the in situ carcinomas of low grade [35, 36]. The total plasma concentration of androgens does not seem to change in prostate cancer patients, even though free testosterone may be augmented due to the significant reduction of sex hormone-binding globulin [37]. Several genetic and epigenetic mechanisms have been proposed to explain the local increased activity of androgens. They involve germinal or somatic AR alterations leading to protein stabilization, activating mutations, or splicing variants [38]. A polymorphism due to the shortening of the CAG repeat length in the N terminal domain of AR in Afro-Americans, increasing its transcriptional activity, might explain the higher prostate cancer risk of this population [39]. An altered balance between increased expression of AR co-activators [40, 41] and decreased expression of co-repressors can also enhance sensitivity to androgens. Interestingly, progression to hormone resistance in prostate cancer is generally not due to an AR loss but to a ligand-independent increased AR activity via different mechanisms such as gene amplification [42], activation upon phosphorylation by MAP or PI3 kinases [43], activating mutations [38], or epigenetic demethylation of co-activator promoter [41].

PRs in Breast Cancer

In contrast to androgens in prostate cancer, the role of an increased PR activity in breast carcinogenesis is more debatable. First, breast cancers are very heterogeneous and only the luminal type expressing PR are potentially responsive to progestins. Secondly, while the bad prognostic significance of an increased FASN protein level has been shown in several studies, [27, 28], the role of progesterone and progestins in breast cancer has been debated [44] based on different results according to the experimental systems. In human cancer cell lines (MCF7, T47 D) cultured on plastic, progestins inhibit rather than stimulate cell division. This could be due to their anti-estrogenic activity [45] and/or to triglycerides accumulation in lipid droplets observed in T47 D cells [46]. However, in normal human mammary glands growing within a Matrigel matrix [47], progesterone appears to be mitogenic, and lipid droplets generally do not accumulate in vivo in breast or prostate cancer [36]. Actually, epidemiological studies strongly suggest that progestins stimulate breast carcinogenesis. The different HRTs of menopause indicate that the addition of synthetic progestins, administered together with estrogens to prevent endometrial cancer, increases the risk of breast cancer compared to estrogens alone [2, 48]. Several explanations have been proposed for the marked discrepancy between results obtained in vitro and in patients: in vivo, a paracrine regulation of cell growth by progestins [49] and/or the induction of proteins crucial for cell survival such as FASN and VEGF via angiogenesis [50], which provide nutrients to cancer cells, can also explain the co-carcinogenic and tumor promoter effect of progestins. These proteins may not be as necessary in vitro than they are in vivo. It has also been proposed that progestins might reactivate cancer stem cells [51] or stimulate progenitor cells in normal breast [47]. Finally, the effect of progestins may be different on normal or transformed mammary glands.

While PR level in breast cancer tissue as measured by ligand binding assay, generally increasing after menopause, very few studies have compared PR level in normal, proliferating cells and in cancer situ (CIS) mammary cells. By immunohistochemistry, in studying the early stages of breast carcinogenesis, we detected a statistically significant increased level of PR and FASN level in proliferating breast lesions in comparison to adjacent normal tissues [52] (Fig. 3). At later pre-invasive stages, FASN level continued to increase to reach a maximum in CIS, while PR decreased. The progesterone-induced FASN regulation observed at a low level in normal mammary glands increased significantly as early as non-proliferative breast lesions. It was then bypassed in later steps of carcinogenesis by other stimuli, possibly involving higher activity of the MAP kinase and/or PI3Kinase/Akt pathways frequently detected in high risk
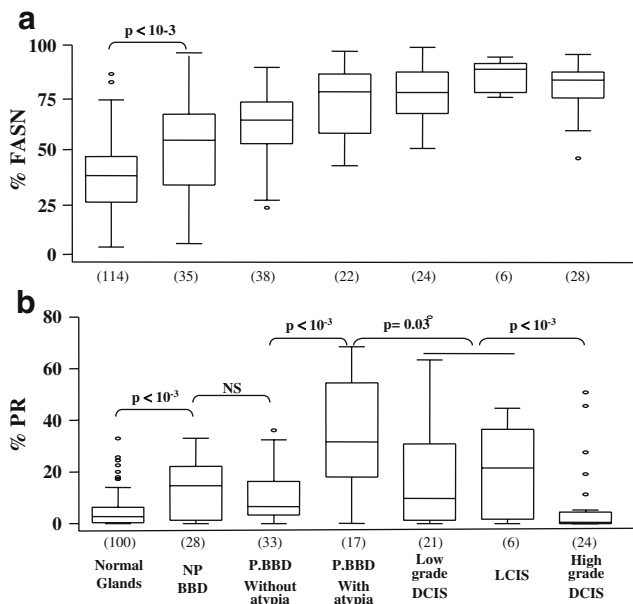
Fig. 3 FASN (**a**) and progesterone receptor (*PR*) (**b**) expression in mammary lesions with increasing breast cancer risk compared to the adjacent "normal" glands. Expression levels of FASN and PR proteins were estimated by immunohistochemistry and a computer-aided image analyzer. They are represented in *Box plot graphs*; each box contains the interquartile range values, the *central line* indicating the median value, the *vertical lines* representing the nonparametric 95% confidence interval, excluding outliers (*circles*). The statistical significance of the differences is indicated in the figure. *NS* not significant, when $p >$ 0.05 according to the nonparametric Kruskal–Wallis test. The number of each pooled structures is presented in *brackets*. *NPBBD* nonproliferative benign breast disease, *PBBD* proliferative BBD, *DCIS* ductal breast carcinoma in situ, *LCIS* lobular carcinoma in situ. FASN expression increased progressively in lesions with increased breast cancer risk, but was already significant in NPBBD. PR expression increased in early lesions, was maximal in PBBD with atypia, but was low in high-grade DCIS which may not be the precursor of PR-positive luminal breast cancers. Reproduced from [52].

lesions [53]. Accordingly, we found that FASN and HER2/Neu upregulation were strongly correlated in high-grade DCIS [52] as it is in the HER 2/Neu invasive breast cancers [54].

Other mechanisms than increased PR level can facilitate progesterone activity, such as gene amplification of the co-activator *AIB1* [55], an unbalance in breast cancer between the two PR isoforms A and B [56], or a decreased level of a competitor. In this respect, the wild-type BRCA1 in in vitro transfected model competes with PR on PRE of progestin-regulated genes [57]. The inactivation of BRCA1 by haploinsufficiency or mutations may also increase PR activity by decreasing its inhibitory effect.

Androgens in Breast Cancer

Androgens, in the T47D human breast cancer cell line expressing the three sex steroid receptors, can also bind PR and upregulate FASN expression. However, FASN induc-tion was only observed at high androgen concentrations and was inhibited by both RU486 and flutamide, suggesting an action via PR and AR. Androgens induce specifically via its own receptor the synthesis of other proteins which are inhibited by flutamide, but not by RU486 [18]. Two of them were identified as the GCDFP 15 and the Zn alpha 2 glycoprotein (ZAG) [58], a lipid-mobilizing factor which decreases the triglyceride reserves in the body [59]. Whether ZAG contributes to prevent triglyceride accumulation in cancer cells is unknown. Interestingly, a transcriptome study of breast tumors has identified a molecular apocrine subtype of breast cancer within the ER-negative breast cancers [60]. These apocrine ER-negative breast cancers display a poor prognosis and express AR, androgen-regulated genes, including those associated with lipogenesis and HER2/Neu which is associated with high FASN expression [4, 54].

Hormone-Resistant Prostate and Breast Cancers

In hormone-resistant prostate and breast cancers, increased level and/or activity of oncogenes that in turn superactivate MAP kinase and PI3 kinase/Akt pathways became predominant to stimulate FASN expression and lipid synthesis. These pathways not only increase cell proliferation but also FASN and lipid synthesis via SREBP induction [53] and/or PR and AR phosphorylation, leading to their ligand-independent activation [34, 43]. These mechanisms are preponderant during tumor progression toward hormone resistance, mostly in breast cancer; however, they have also been reported in earlier stages. They are also directly observed in the hormone-resistant HER2/Neu and triple-negative clusters of breast cancers. In these cases, growth factor activation of MAP kinase and PI3 kinase signaling pathways appears to take over from the sex steroid signaling pathway.

Consequences of the Lipogenic Phenotype of Cancer Cells and Clinical Potential of its Inhibition

Increased In Situ Lipogenesis Gives a Selective Advantage to Cancer Cells to Establish a Colony and to Grow in a Poorly Vascularized Tumor

FASN is required for normal embryonic development as shown by gene invalidation in mice [61]. In hormone-dependent cancers, the role of sex steroids in stimulating DNA replication and cell division has been extensively studied. However, cells cannot multiply in the absence of fatty acids which are generally provided by the circulation in normal but not in most cancer cells. In most solid tumors, angiogenesis and lymphangiogenesis are not adequate to

bring nutrients and oxygen to the tumor [62]. This condition occurs both during the early stages of carcinogenesis, when the proliferating small-volume tumors, CIS, or small metastases are not yet vascularised, and in larger tumors which are vascularised only at the periphery [6, 62]. Therefore, endogenous FASN expression is needed not only for the survival and growth of these tumors to build new membranes required for the continuously proliferating cancer cells but also to produce signaling lipids. For instance, FASN overexpression is associated with palmitoylation of WNT1 and cytoplasmic stabilization of β-catenin in prostate cancer [63]. FASN expression then progressively increases during cancer progression to reach its higher level in hormone-independent cancers [53, 64].

New Therapeutic Approaches of Cancer by FASN Inhibitors

Since normal cells do not require FASN activity, FASN inhibitors should be less or not toxic in normal cells and specifically active in cancer cells in which FASN is upregulated.

Several studies have reported a decreased proliferation and increased apoptosis of cancer cells upon inhibition of FASN activity or production both in vitro and in vivo in human mammary tumor xenografts in nude mice [65, 66]. The effect of FASN chemical inhibitors is mediated, at least in part, by the intermediate metabolite malonyl CoA whose accumulation increases apoptosis in cancer cells. However, it is also due to the decrease of FA synthesis since the effects of FASN inhibitors (cerulenin, C75) and FASN siRNA are suppressed by palmitic acid addition. Recently, less toxic drugs were developed such as synthetic polyphenols which induce cancer cell apoptosis by inhibiting FASN activity [67]. This approach, eventually associated to other nontoxic inhibitors, such as proteasome inhibitors [68] or angiogenesis inhibitors, appears to be promising.

Sex Steroid Antagonists Also Inhibit In Situ Lipogenesis in Hormone-Dependent Cancers

These antagonists are widely used in the therapy of human hormone-dependent cancers. They inhibit the mitogenic activity of sex steroid hormones and some of them might also block in situ lipogenesis, at least during the early steps of tumor progression. Moreover, as the early steps of carcinogenesis are characterized by increased activity of AR in prostate and of PR in breast, anti-androgens and anti-progestins are also being considered for the prevention of these cancers in high-risk patients. Studies in mice suggest that progestin inhibitors may be used for breast cancer prevention in subjects carrying BRCA1 mutations, but this hypothesis is not yet validated in the clinic [69].

Action Via Other Nuclear Receptors

PPAR γ activators [32, 70, 71] and vitamin D3 receptor [33] are other therapeutic and preventive targets of prostate cancer whose activation by their ligands prevents in situ FASN synthesis, most likely by inhibiting androgen action (see third part of "Regulation of Fatty Acid Synthase by Sex Hormones in Breast and Prostate Cancers").

Moreover, several natural polyphenols and flavonoids, found in green tea, fruits, and soy (genistein) are also proposed for the prevention of hormone-dependent cancers because of their good tolerance. Among other mechanisms, they also interfere on FASN synthesis either directly [72] or via their anti-androgenic action [73]. Their FASN inhibitory effect can be mediated by their downregulation of SREBP1 [74] or by binding to PPARγ as described with high doses of genistein, which may explain the protective effect of these doses on hormone-dependent cancers [75].

Conclusions

Sex steroid hormones play a major role as tumor promoters in both breast and prostate cancers to stimulate DNA replication. Androgens and progesterone are also involved in the development of the lipogenic phenotype of cancer cells via the induction of proteins and enzymes such as FASN required for their autonomous nutrition. The role of FASN induction by sex steroids in facilitating cell nutrition and membrane synthesis required for continuously dividing cancer cells may therefore be as important in vivo as the stimulation of cell cycle, mostly due to estrogens in breast and androgens in prostate. While increased lipogenesis is widely observed in most solid tumors, the effect of sex steroid receptors on FA synthesis pathways is obviously limited to hormone-dependent cancers. We propose that an increased activity of the steroid receptors (AR and PR) is partly responsible for the in situ overexpression of the key enzymes involved in FA synthesis, at least in the early and hormone-dependent stages of tumorigenesis. This hypersensitivity to androgens and progesterone (but also to the mitogenic estrogens via other mechanisms) would then facilitate tumor growth (Fig. 2). In addition to a decreased activation of nuclear receptors (vitamin D3, PPARγ) involved in the downregulation of FA synthesis, several pieces of evidence indicate that upregulation of AR and PR level and/or activity is involved in the stimulation of FASN expression. Increased FA synthesis is another example of cancer cell addiction [76]. In sporadic cancers, this addiction may be due to gene mutation but also to acquired epigenetic alterations [77]. While most of the current biological therapies are targeted at mitogenic receptors, we believe that there is a potential to inhibit in situ lipid

synthesis in order to starve specifically cancer cells by blocking their source of lipids.

Conflict of interest We declare no conflict of interest.

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