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Review Article

# Lipid metabolism and cancer progression: The missing target in metastatic cancer treatment

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ABSTRACT

There is a renewed interest in metabolism alterations and its impact on cancer development and progression. The metabolism of cancer cells is reprogrammed in order to support their rapid proliferation. Elevated fatty acid synthesis is one of the most important aberrations in cancer cell metabolism, and is required both for carcinogenesis and cancer cell survival. We have previously shown that cancer cells explore metabolic pathways especially autophagy and particularly enhanced glycolysis and suppressed oxidative phosphorylation to promote treatment resistance. To support cell proliferation in cancer, lipid metabolism and biosynthetic activities is required and often up-regulated. Here we bring lipid metabolic pathways into focus and summarized details that suggest a new perspective for improving chemotherapeutic responses in cancer treatment, and indicate the need to design more inclusive molecular targeting for a better treatment response.



## Introduction

The earliest report of Otto Warburg about 100 years ago that cancer cells exhibited dysregulated metabolism compared with normal cells, lead to a hypothesis that molecular oxygen defects in cells results in a slow adaptation to enhanced aerobic glycolysis and may constitute a metabolic switch that caused cancer (Warburg, 1956). The enhanced aerobic glycolysis exhibited by some cancer cells provides them with a characteristic signature and results in increased dependence on glucose (Omabe et al., 2013). Thus, Warburg effect is a distinctive feature of many human and animal tumors (Omabe et al., 2013). In majority of cancers, glucose is converted mostly to lactate (Fig. 1), and, therefore, only 2 moles of ATP per 1 mole of glucose are synthesized, which is therefore insufficient for

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cancer cells to cope with its energy requirements. However, in most non-cancer cells, the mitochondria produce $CO_2$ and $H_2O$ from glucose, and 38 moles of ATP are synthesized per 1 mole of glucose from the oxidative metabolism under aerobic conditions (Omabe et al., 2013).

### *From glucose metabolism to fatty acid biosynthesis*

Full detail of glucose metabolism can be found in appropriate textbook of Biochemistry. The understanding of metabolism forms a unique component of practice for Chemical Pathologist. In brief, following cellular uptake by glucose transporters, glucose is phosphorylated by hexokinases to glucose-6-phosphate (Figs. 1 and 2). Most of glucose-6-phosphate enters the glycolytic pathway to generate pyruvate and ATP. Pyruvate is converted to acetyl coenzyme A (CoA), and enters the citric acid cycle in the mitochondria (Omabe et al., 2013). Depending on the oxygen availability citrate can be fully oxidized to generate ATP by oxidative phosphorylation, or it can be transported to the cytoplasm where it is converted back to acetyl-CoA (the requisite building block for fatty acid (FA) synthesis) by ATP citrate lyase (ACLY). Under anaerobic conditions pyruvate can also be used as an electron acceptor, resulting in the lactate dehydrogenase (LDH)-catalyzed production of lactate, which is secreted from the cell. A portion of the acetyl-CoA is carboxylated to malonyl-CoA by acetyl-CoA carboxylase (ACACA), the primary rate-limiting enzyme and site of pathway regulation. Fatty acid synthase (FASN), the main biosynthetic enzyme, performs the condensation of acetyl-CoA and malonyl-CoA to produce the 16-carbon saturated FA palmitate and other saturated long-chain FAs, which is dependent on NADPH as a reducing equivalent. NADPH (which is essential for FA synthesis) is provided in a reaction catalyzed by malic enzyme, or can be acquired through the pentose phosphate pathway. Saturated long-chain FAs can be further modified by elongases or desaturases to form more complex FAs, which are used for the synthesis of various cellular lipids such as phospholipids, triglycerides and cholesterol esters, or for the acylation of proteins. Elevated activities of citrate synthase (CS) and ACLY are observed in some malignancies, hence, inhibition of ACLY is known to lead to cessation of tumor growth (Schlichtholz et al., 2005; Vazquez-Martin et al., 2009). This is because cell proliferation requires a constant supply of lipids and lipid precursors to fuel membrane biogenesis and protein modification. In this review, we searched a number of available literatures through Medline, pub med, Google scholar and EMBO search engine using key words like cancer metabolism, fatty acid, cytokines and metastasis. This work therefore highlights a synthesis, and focused on the role of adipocytes derived molecules and lipid metabolism in cancer progression, and underscored current understanding toward exploring this physiologic phenomena

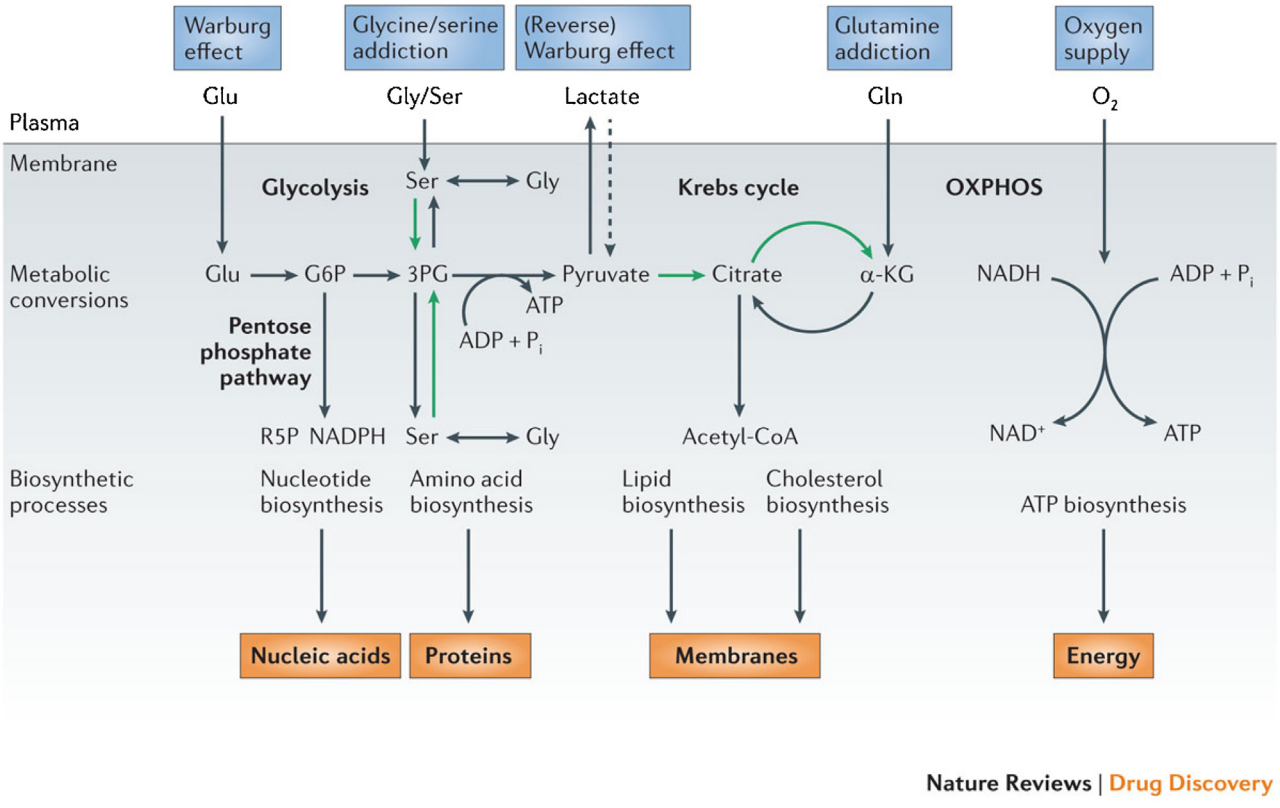


**Fig. 1 – Malignant cells exhibit a profound imbalance toward anabolic metabolism. Cancer cells take up high amounts of glucose (Glu; underpinning the Warburg effect) and glutamine (Gln) and divert them to the phosphate pentose pathway and lipid biosynthesis, respectively. Coupled to an increased uptake of glycine (Gly) and serine (Ser), which are required for protein synthesis and sustain anaplerotic reactions that replenish Krebs cycle intermediates, this generates sufficient building blocks (that is, nucleic acids, proteins and membranes) for proliferation.**
***Source:*** **Adapted from Galluzzi et al. (2013).**

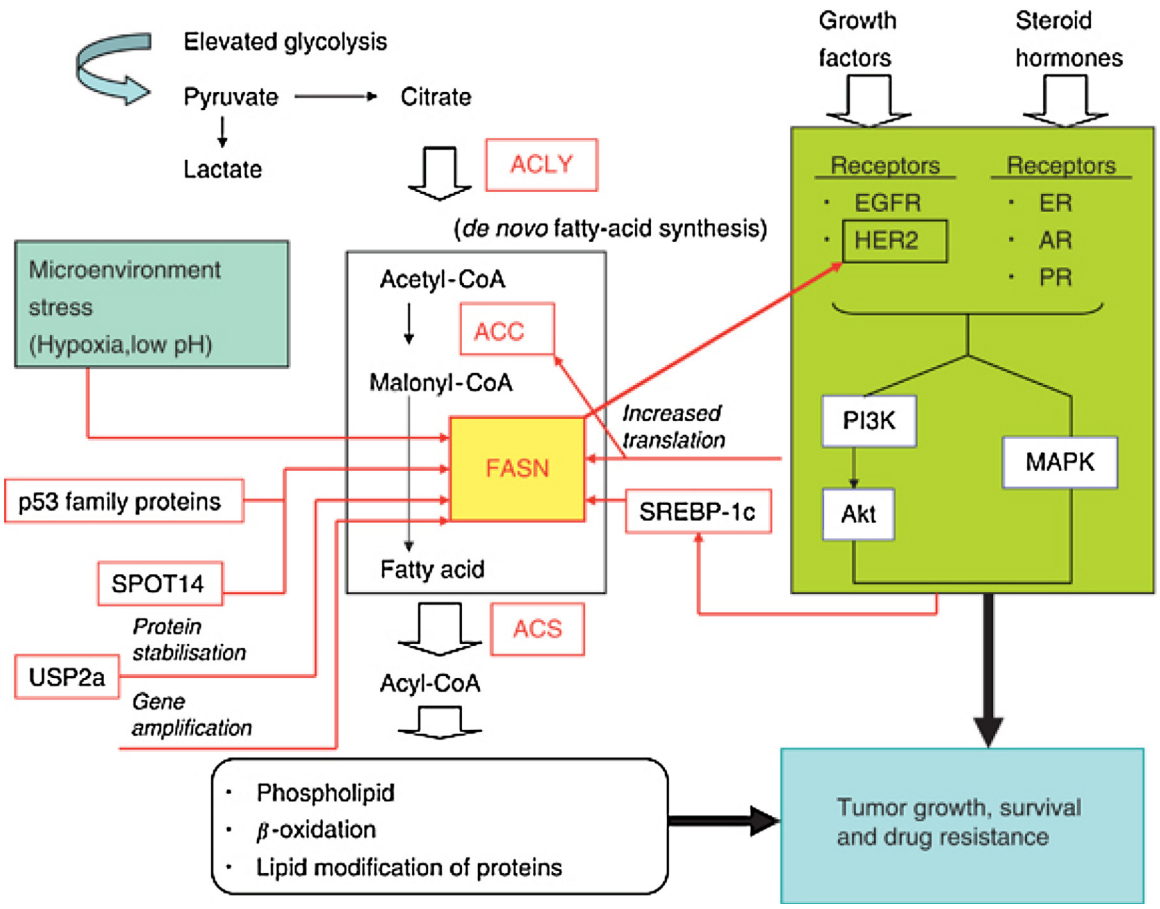


**Fig. 2 – illustrating elevated fatty-acid metabolism with growth factor signaling in cancer in cancer cells play essential roles including tumor-related FASN overexpression. FASN and ACLY, PI3K are all SREBP -1c regulated in cancer cells. Hypoxic tumor microenvironment, as well as multiple other factors are involved in FASN overexpression and elevated lipogenesis in cancer. ACLY, ATP citrate lyase; ACC, acetyl-CoA carboxylase; FASN, fatty-acid synthase; ACS, acyl-CoA synthetase; EGFR, epidermal growth factor receptor; ER, estrogen receptor; AR, androgen receptor; PR, progesterone receptor; PI3K, phosphatidylinositol-3-kinase; MAPK, mitogen-activated protein kinase; SREBP-1c, sterol regulatory element-binding protein 1c; USP2a, ubiquitin-specific protease-2a.**
***Source:*** **Adapted from Mashima et al. (2009).**

in designing and developing next generation treatment target for cancer control.

Details discussed in this review suggest that lipid metabolism and indeed adipocyte derived products may important molecular target for better cancer treatment.

### *Hypoxia controls the metabolic switch*

The switch of cellular metabolism from mitochondrial respiration to anaerobic glycolysis is a recognized hallmark of cancer cells and associated with tumor malignancy (Lu et al., 2008; Omabe et al., 2013). However, the mechanism of this metabolic switch remains largely unknown. Interestingly, some tumors display a diminished flux of glucose carbon through PDH-catalyzed reaction, due to increased PDHK (pyruvate dehydrogenase kinase) activity, under the influence either hypoxia or oncogenic factors. In fact Lu et al. (2008) showed that hypoxia-inducible factor-1 (HIF-1) induced pyruvate dehydrogenase kinase-3 (PDK3) expression leading to inhibition of mitochondrial respiration and increased lactic acid accumulation and drugs resistance. Whereas knocking down PDK3 inhibited hypoxia-induced cytoplasmic glycolysis and cell survival (Lu et al., 2008). These suggests that increased PDK3 expression due to elevated HIF-1alpha in cancer cells may play critical roles in metabolic switch during cancer progression and chemo resistance in cancer therapy and points to a possible use of carbon source other than glucose, to fill up its increasing lipid requirement. Data from a western blot analysis demonstrated that PDK3 was markedly increased in colon cancer compared to cells in adjacent normal tissues, and that PDK3 expression was positively correlated HIF-1α, a known cause of treatment failures and cancer progression (Omabe et al., 2011). Therefore, the implication of hypoxia mediated mitochondrial dysfunction has been shown to be a loss of ability to trigger apoptosis, and a gain in survival advantage and mutagenic damage to DNA (Omabe and Odii, 2013).

### *Oncometabolites mediate hypoxia responses*

The oncogenic roles of 2-hydroxyglutarate ((R)-2HG), succinate and fumarate have been reported (Adam et al., 2014). While (R)-2HG is a product of gain-of-function mutations in the cytosolic and mitochondrial isoforms of isocitrate dehydrogenase (IDH), succinate and fumarate are intermediates of the Krebs cycle. Loss-of-function mutations in the tumor-suppressor genes succinate dehydrogenase (SDH) and fumarate hydratase (FH) cause intracellular accumulation of succinate and fumarate, respectively (Adam et al., 2014). These three oncometabolites (R)-2HG, succinate and fumarate are sufficiently similar in structure to 2-oxogluratate (2OG) and inhibit a range of 2OG-dependent deoxygenates, including hypoxia-inducible factor (HIF) prolyl hydroxylases (PHDs), histone lysine demethylases (KDMs) and the ten-eleven translocation (TET) family of 5-methylcytosine (5mC) hydroxylases, leading to HIF-mediated hypoxia responses and alterations in gene expression through global epigenetic remodeling (Omabe et al., 2011; Adam et al., 2014); that may contribute to malignant transformation. In addition, the (R)-2HG alone has been shown in some settings to act as a co-substrate for PHD2 in the prolyl hydroxylation of HIF1α, leading to cellular transformation as a result of reduced HIF expression, while fumarate can irreversibly modify cysteine residues in proteins via succination, leading to transcription of genes involved in antioxidant response (Adam et al., 2014). Fumarate accumulation may also impact on cytosolic pathways potentially hampering the urea and purine nucleotide cycles (Adam et al., 2014).

### *The adipocytes and adipose-derived proteins*

Fatty acid synthase (FASN) reaction constitutes the last step in palmitate synthesis. Fatty acids produced by FASN are in excess of cell requirements, and are stored in the adipocytes. Increasing mass of adipocytes in an individual results in obesity. The increasing prevalence of obesity is of great concern for public health as it is known to be a major contributor to the global burden of disease. The prevalence of overweight, defined as a body mass index (BMI, weight/height) of 25–29 $kg/m^2$, and obesity, BMI ~30 $kg/m^2$, has been rapidly increasing during recent decades in both developed and developing countries. In the US and Europe, obesity affects approximately 15–25% of men and 10–35% of women.

There are two types of adipose tissues, white adipose tissue (WAT) and brown adipose tissue (BAT). Adipose tissue is composed of various cell types: lipid-laden mature adipocytes and the remaining stoma vascular fraction (SVF) that includes blood cells, endothelial cells, and macrophages (Weisberg et al., 2003). In fact, adipose tissue is an important endocrine organ that secretes many biologically active substances, such as leptin, adiponectin, tumor necrosis factor α (TNF-α), and monocyte chemo attractant protein 1 (MCP-1), which are collectively termed adipocytokines (Weisberg et al., 2003). The physiologic role of these adipose-derived proteins are not fully understood, while some cytokines have both immunomodulatory functions and act as systemic or auto-/paracrine regulators of metabolism, others such as leptin and adiponectin are regulators of both metabolism and inflammation (Juge-Aubry et al., 2005) (see Fig. 3).

## Adipocyte derived factors and cancer progression

In ovarian cancer, Nieman et al. (2011) demonstrated that primary human omental adipocytes promoted homing, migration and invasion of ovarian cancer cells, and that adipokines including interleukin-8 (IL-8) mediate these activities. In fact, adipocyte-ovarian cancer cell coculture resulted in direct transfer of lipids from adipocytes to ovarian cancer cells and promoted *in vitro* and *in vivo* tumor growth (Nieman et al., 2011). Furthermore, mechanistic studies from *in vitro* experiments showed that coculture induced lipolysis in adipocytes and β-oxidation in cancer cells, suggesting that adipocytes act as an energy source for the cancer cells (Nieman et al., 2011). A protein array identified upregulation of fatty acid-binding protein 4 (FABP4, also known as aP2) in omental metastases as compared to primary ovarian tumors, and that FABP4 expression was detected in ovarian cancer cells at the adipocyte-tumor cell interface, and FABP4 deficiency substantially impaired metastatic tumor growth in mice, indicating that adipocytes derived factors including FABP4 has a key role in ovarian cancer metastasis (Nieman et al., 2011). These data indicate adipocytes provide fatty acids for rapid tumor growth, identifying lipid metabolism and transport as new targets for the treatment of cancers where adipocytes are a major component of the microenvironment.

In breast cancer, evidence from two-dimensional coculture experiments showed that murine and human tumor cells cocultivated with mature adipocytes exhibit increased invasive capacities *in vitro* and *in vivo*, using an original (Dirat et al., 2011) the authors also demonstrated that adipocytes cultivated with cancer cells exhibit an altered phenotype in terms of delipidation and decreased adipocyte markers associated with the occurrence of an activated state characterized by over expression of proteases, including matrix metalloproteinase-11, and proinflammatory cytokines [interleukin (IL)-6, IL-1β] (Dirat et al., 2011). In fact Dirat and Colleagues in 2011 clarified using both *in vitro* and *in vivo* evidence that (i) invasive cancer cells dramatically impact surrounding adipocytes; (ii) peritumoral adipocytes exhibit a modified phenotype and specific biological features sufficient to be named cancer-associated adipocytes (CAA); and (iii) CAAs modify the cancer cell characteristics/phenotype leading to a more aggressive behavior. Thus strongly pointing that that adipocytes participate in a highly complex vicious cycle orchestrated by cancer cells to promote tumor progression that might be amplified in obese patients, indicating that novel therapy designed toward targeting adipocytes derived factors may become the next generation cancer treatment and chemoprevention. This is supported by a number of published studies in the literature. For instance, reprogrammed adipocytes have been shown to provide growth factors and fuel to cancer cells, promoting metastasis, and sustaining uncontrolled growth (Ribeiro et al., 2012). Ribeiro et al. (2012) have shown that peri-prostatic (PP) adipose tissue

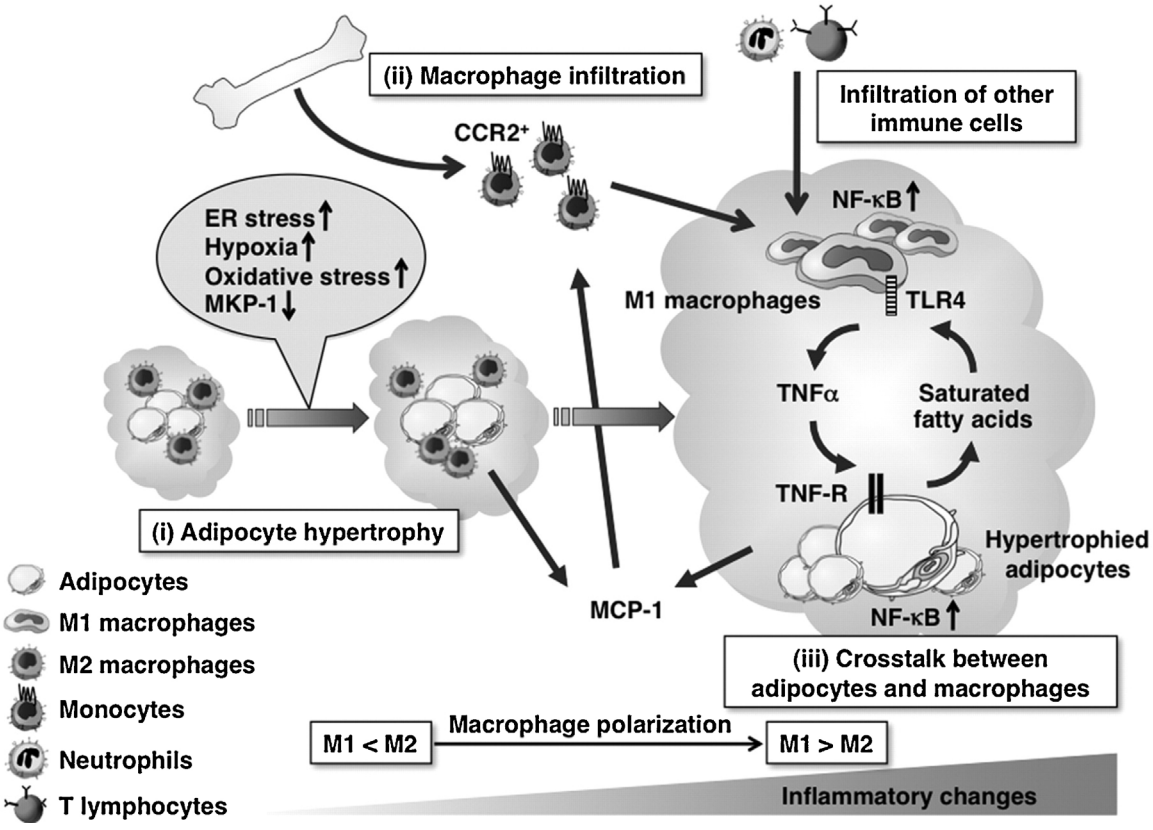


**Fig. 3 – Molecular mechanism underlying adipocyte, macrophages interaction and inflammation and cancer. increased metabolic stresses such as hypoxia, and oxidative stress and down-regulation of MKP-1 are involved in the induction of inflammatory changes in adipocytes during the course of adipocyte hypertrophy. T lymphocytes, and macrophages, infiltrate into obese adipose tissue (ii) and thus, enhance the inflammatory changes through the crosstalk with parenchymal adipocytes (iii). For example, the macrophage-derived TNF-α induces the release of saturated fatty acids from adipocytes via lipolysis, which in turn, induces inflammatory changes in macrophages via TLR4. Such a paracrine loop between adipocytes and macrophages constitutes a vicious cycle, thereby accelerating further adipose tissue inflammation. Recent evidence has also pointed to the heterogeneity of adipose tissue macrophages; i.e., M1 or ''classically activated'' (proinflammatory) macrophages and M2 or ''alternatively activated'' (anti-inflammatory) macrophages. Infiltrated macrophages exhibit a phenotypic change from M2 to M1 polarization in obese adipose tissue, thereby accelerating adipose tissue inflammation. TNF-R, TNF-α receptor.**
***Source:*** **Adapted from Suganami and Ogawa (2010).**

explants from overweight/obese prostate cancer patients had significantly elevated matrix metalloproteinases 9 MMP9 activity, which is correlated with disease progression and metastasis (Ribeiro et al., 2012). When PC-3 cells were stimulated with condition medium from PP adipose tissue explants, increased proliferative and migratory capacities resulted on the other hand, when LNCaP cells are stimulated with PP explants condition medium enhanced cancer cell motility resulted (Ribeiro et al., 2012). Put together, these studies concluded that PP adipose tissue may play an important role by releasing cytokines and growth factors, such as interleukin-6 and matrix metalloproteinases, that may promote tumor cell proliferation and migration. These interactions may have a key-role in determining prostate cancer aggressiveness and progression. Thus, it appears therefore that cross-talk'' mechanism may exist between adipose tissue and cancer cells that may ultimately result in more aggressive prostate cancer and promote disease progression, especially in obese patients.

## Oncophospholipid; resources for cell lipid membrane biosynthesis

Fatty acid synthesis is energetically expensive, requiring ATP, NADPH and redirection of acetyl-CoA from oxidative pathways, where it would produce ATP, to lipogenesis. It is not clear if cancer cells prefer using fatty acid produced endogenously through FASN or exogenously.

### *Endogenous fatty acid resources*

It is generally accepted that many types of tumor including breast cancer cells endogenously synthesize 95% of fatty acids

(FAs) de novo, despite having adequate nutritional lipid supply. Evidence from published studies indicates that activation of endogenous FA biosynthesis was sufficient to significantly enhance breast epithelial cell proliferation and survival (Vazquez-Martin et al., 2008). When analysing molecular mechanisms by which acute activation of de novo FA biosynthesis triggered a transformed phenotype, it was shown that HBL100 cells, transiently transfected with pCMV6-XL4/FASN, to enhance their endogenous lipid synthesis, were found to exhibit a dramatic increase in the number of phosphor-tyrosine (Tyr)-containing proteins, especially among the key members of the HER family (erbB) network, which were found switched-off in mock-transfected HBL100 cells (Vazquez-Martin et al., 2008). Further analysis from that study suggested that FASN over activation significantly increased (>200%) expression levels of epidermal growth factor receptor and HER2 proteins in HBL100 cells, and confirmed that acute activation of endogenous FA biosynthesis specifically promoted hyper-Tyr-phosphorylation of HER1 and HER2 in MCF10A cells; which triggered HER1/HER2-breast cancer-like phenotype (Vazquez-Martin et al., 2008). This suggests that exacerbated endogenous FA biosynthesis in non-cancerous epithelial cells may be sufficient to induce a cancer-like phenotype.

### *Exogenous fatty acid resources*

Recently, it has been shown that show that cancer cells and tumors robustly incorporate and remodel exogenous palmitate into structural and oncogenic glycerophospholipids, sphingolipids, and ether lipids; and that fatty acid incorporation into oxidative pathways was reduced in aggressive human cancer cells, and instead shunted into pathways for generating structural and signaling lipids, suggesting that cancer cells do not solely rely on de novo lipogenesis, but also utilize exogenous fatty acids for generating lipids required for proliferation and protumorigenic lipid signaling (Louie et al., 2013). In fact, by comparing the rate of incorporation of exogenously fatty acid, palmitate and endogenous fatty acid, acetate, in MCF-10A, non-transformed human breast epithelial cells, and MCF-7 (ER+) and MDA-MB-231 (ER−) human breast cancer cells, Hopperton et al. (2014) showed that cancer cell lines incorporated 2–3 fold more radioactive acetate into their total lipids than the non-cancer cells, reflecting a higher rate of endogenous fatty acid synthesis. This suggests that cancer cells explore both the endogenous and exogenous lipid resources to promote phospholipid requirements to sustain cell survival advantage. In addition, it appears that the increased usage of exogenous fatty acid by cancer cells is for used in supporting membrane synthesis. For example evidence from experimental studies have shown that cancer cell lines incorporated a significantly higher proportion of exogenous palmitate into ChoGpl – a predominant component of cell membranes, compared to fatty acids derived endogenously from acetate (Hopperton et al., 2014). This selectivity for exogenously-derived fatty acids for membrane synthesis does not support the notion that endogenously synthesized fatty acids are either required for, or specifically directed toward, membrane synthesis in cancer cells. It appears that endogenously synthesized fatty acids may be utilized in the same ways as those supplied exogenously, given that that cancer cells do not seem to have a preference for endogenously synthesized fatty acids (Hopperton et al., 2014). Thus phospholipid composition of cancer cell membranes, may depends on the identity and quantity of exogenous fatty acids as well as those synthesized endogenously (Hopperton et al., 2014). This suggest, that therapy targeting on the endogenous sources of fatty acid may fail since the cancer cells depend more on exogenous source of fatty acid for synthesis of cell membrane lipids.

## Adipocytes interacts with cancer microenvironment

From practice point of view, cancers occur in close proximity to adipose tissue. This is often seen in cancer of the breast, colon, pancreas, ovary, uterus, and liver which are all surrounded by and/or infiltrated by adipose tissue. Extension of these cancer types outside of their originating organ often takes them into direct contact with adipose tissue. Furthermore, adipocytes are found in the bone marrow, a common site for solid tumor metastasis (Aldhafiri et al., 2014).

Bone marrow adiposity is not only affected by obesity but also has recently been shown to be influenced by ALL treatment. Vicente López et al. isolated mesenchymal stem cells (MSCs) from bone marrow aspirates of ALL patients at various time points: diagnosis, during therapy, and after therapy, and showed that ALL-MSC from treated patients had an increased adipogenic differentiation potential, including a higher expression of adipogenic genes (CEBP and PPAR-gamma), compared to healthy MSC (Vicente López et al., 2014) another study also demonstrated that whenever syngeneic ALL cells were implanted into mice by a retro-orbital injection, clones of infiltrated adipose tissue were found within 10 days, at a similar degree as other more classic sites for ALL, such as spleen and liver, indicating that the cancer cells migrate toward adipocytes; this action could perhaps be mediated by adipocyte secretion of stoma cell-derived factor 1 alpha (SDF-1α or CXCL12) (Pramanik et al., 2013). Generally, obesity is not known to be associated with increased serum levels of SDF-1α; however, there are indications that obese mice have a significantly higher burden of leukemia cells in visceral fat compared to control mice (Pramanik et al., 2013). Put together, it appears that adipocytes may facilitate cancer microenvironment including bone marrow engraftment via secretion of adipocytes derived factors like SDF-1α and leptin (Fig. 3).

### *Adipose tissue and carcinogenesis; leukemia, clinical evidence*

From the forgoing, efforts have been spent to illustrate the role of adipose tissue and adipocytes in supporting progression of several types of cancer. Bone marrow, a major site of metastasis for solid tumors and an important microenvironment for hematological malignancies, is also rich in adipocytes. In fact, after induction chemotherapy for acute lymphoblastic leukemia (ALL), adipocytes can represent the primary cellular component of bone marrow which is easily visualized under microscope. Given the effects of obesity on

cancer prognosis, one can ask if fat cells may have a role in leukemias as in other cancers. Several studies have found an increased risk of developing leukemia among the obese, for example, a meta-analysis of cohort studies, Larsson and Wolk found that excess body weight was associated with an increased risk of developing all four major subtypes of hematologic malignancies [ALL, acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myelogenous leukemia (CML)] (Larsson and Wolk, 2008). The author showed that compared with nonoverweight individuals (BMI < 25 kg/m($^2$)), that relative risks (RRs) of leukemia were 1.14 [95% confidence interval (CI), 1.03–1.25] for overweight individuals (BMI 25–30 kg/m($^2$)) and 1.39 (95% CI, 1.25–1.54) for obese (BMI ≥ 30 kg/m($^2$)) individuals, and that a continuous scale of 5 kg/m($^2$) increase in BMI was associated with a 13% increased risk of leukemia (RR, 1.13; 95% CI, 1.07–1.19) (Larsson and Wolk, 2008). In addition In a meta-analysis of 4 studies reporting results on subtypes of leukemia, also found RRs associated with obesity of 1.25 (95% CI, 1.11–1.41) for chronic lymphocytic leukemia, 1.65 (95% CI, 1.16–2.35) for acute lymphocytic leukemia, 1.52 (95% CI, 1.19–1.95) for acute myeloid leukemia and 1.26 (95% CI, 1.09–1.46) for chronic myeloid leukemia (Larsson and Wolk, 2008). This clearly suggest that that excess body weight is associated with an increased risk of developing leukemia and that a 5 kg/m$^2$ of increased BMI is associated with a 13% increase risk of developing leukemia. Others have shown that obesity increases the risk of developing Hodgkin's lymphoma, non-Hodgkin's lymphoma, and multiple myeloma (Larsson and Wolk, 2011). For example, a meta-analysis of prospective studies on epidemiologic evidence for association of body mass index (BMI) with non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL) incidence and NHL mortality found that BMI was significantly positively associated with risk of diffuse large B-cell lymphoma (RR, 1.13; 95% CI, 1.02–1.26), but not other NHL subtypes; and a RRs of HL of 0.97 (95% CI, 0.85–1.12) for overweight and 1.41 (95% CI, 1.14–1.75) for obesity, indicating that BMI is positively associated with risk of NHL and HL as well as with NHL mortality (Larsson and Wolk, 2011).

### *Adipocytes and treatment outcome in leukemia*

The association between obesity and leukemia prognosis has also been examined in many studies, with some detecting an effect of obesity to worsen prognosis and others finding a conflicting result. For instance, two independent studies acknowledged that their failure to detect an association between BMI and ALL outcomes may have been due to small sample size (Baillargeon et al., 2006; Hijiya et al., 2006). Furthermore, the risk estimates of overall survival and event-free survival from were shown to be worse in overweight/obese patients (Butturini et al., 2007). The largest study was done by the CCG, and included over 5000 children (Butturini et al., 2007). This study found that obesity was associated with a significantly increased risk of relapse, particularly in children over 10 years of age (considered high risk). This finding are in line with the report of another study which included only standard risk patients, and concluded that overweight or obesity at diagnosis was unlikely to impair prognosis (Aldhafiri et al., 2014). Thus, it appears that obesity can impair ALL outcomes at least in high risk, older patients.

## The adipocyte-macrophage cross-talk theory for lipid driven carcinogenesis: adipocyte-derived free fatty acids (FFAs) and macrophages secreted TNF to promote cancer progression

In healthy adults, endogenous fatty acid synthesis takes place in specialized tissues, such as the liver, adipose, cycling endometrium and the lactating breast; these tissues have a lot of fatty acid synthase (FASN) expression. In contrast, over-expression of FASN has been detected in many types of established tumors and pre-malignant lesions. This over-expression appears to confer a survival advantage to cancer cells since it is often associated with advanced cancer stage, metastasis and poor prognosis. The mechanism leading to this survival advantage, however, is not understood.

How does adipose tissue promote inflammation and disease development (see Fig. 3)? The changes that occur in adipose tissue during obesity have been characterized. For example, using microarray analysis, the mass of adipose tissue was shown to be an independent regulator of its gene expression profile (Weisberg et al., 2003). The quantity of transcripts from microarray analysis from mouse adipose tissue was found to correlate significantly with its mass (Weisberg et al., 2003), further analysis in the study revealed three groups of functionally related genes that were collectively regulated by mass. Thirty percent of the transcripts significantly encoded proteins that are characteristically expressed by macrophages; these include the CSF-1 receptor, and the CD68 antigen. In same study, a quantitative RT-PCR experiment also confirmed the expression profile of the five genes identified including (colony-stimulating factor 1 receptor [Csf1r], CD68, Pex11a, Emr1, and Mcp1). Clearly, the study pointed that that macrophage content of adipose tissue may positively correlate with adiposity or its mass. This means that weight gain might be associated with infiltration of fat by macrophages. To understand the role of infiltrated macrophages characterizing the microenvironment of a fat cell, Suganami et al. (2005) developed an *in vitro* coculture system which composed of adipocytes and macrophages, and examined the molecular mechanism whereby these cells communicate. The author showed that coculture of differentiated 3T3-L1 adipocytes cell lines and macrophage cell line RAW264 resulted in marked upregulation of proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-alpha) (Fig. 3), and in downregulation of anti-inflammatory cytokine adiponectin (Suganami et al., 2005). Importantly, the inflammatory changes induced by the coculture occurred without direct contact between the two cell types; pointing to the role of soluble factors (Suganami et al., 2005). To further clarify that soluble factors were secreted by the cells were responsible, the author used a conditioned media experiment and demonstrated that media from RAW264 cells significantly induced MCP-1 ($P < 0.01$), interleukine-6 (IL-6) ($P < 0.05$), and TNF-α ($P < 0.01$) mRNA expression in 3T3-L1; and the media from 3T3-L1 showed no induction of MCP-1 but a significant increase in IL-6 and TNF-α in RAW264 ($P < 0.05$), suggesting

that, TNF-α was mostly derived from RAW264, and only a small amount of TNF-α was secreted from 3T3-L1 (Suganami et al., 2005).

By adding a neutralizing antibody to TNF-alpha, which is a well known cytokine secreted by macrophages; the author observed an inhibition of the inflammatory changes in 3T3-L1, suggesting that TNF-alpha was a major macrophage-derived mediator of inflammation in adipocytes. The author also noted that production of TNF-alpha in RAW264 was markedly increased by palmitate, a major free fatty acid (FFA) released from 3T3-L1, indicating that free fatty acids (FFAs) may be important adipocyte-derived mediators of inflammation in macrophages. Thus, while adipocytes release FFA, macrophages secret TNF-alpha; the two products may form synergy to promote inflammation at various rates, which may compromise a number of biological functions in many ways (see Fig. 3). Put together, it appears there might be a paracrine interaction between adipocytes and macrophages which controls inflammation in adipose tissue *in vivo*; in this state, it is likely mature adipocytes become enlarged in size, and the infiltrated macrophages become increased in number.

### *Adipokines including TNF promotes tumorigenesis*

The biological role of adipokines, such as tumor necrosis factor α (TNF-α), on cell growth and differentiation has been investigated. Using human adipocytes (SW872 and human uterine leiomyoma (HuLM) cells, Nair and Al-Hendy (2011), demonstrated that both SW872-conditioned media and coculture with SW872 cells resulted in increased HuLM cell proliferation significantly ($P < .05$), and by the adding neutralizing antibodies, anti-TNF-α, to SW872-conditioned media cell proliferation of leiomyoma cells was dramatically reversed, and the cells had reduced expression of antiapoptotic marker BCL-2 indicating marked apoptosis. This suggests that TNF-α may be involved in initiation and/or progression of uterine leiomyoma by inducing survival advantage and inhibit apoptosis to the uterine cells. In addition, a study on the effect of human adipocyte cells (SW872) on growth of endometrial glandular epithelial cells (EGE) demonstrated a significant increase in EGE cell proliferation including upregulation of proliferation markers PCNA, cyclin D1, CDK-1, and BCL-2 and decrease in BAK ($P < 0.05$) (Nair et al., 2013). This strongly indicates that adipocytes may have proliferative paracrine effect on EGE cells which may, in part, be mediated via TNF-α; perhaps, by interaction with macrophages as discussed above. From the preceding paragraph, it was clarified that microphages releases 2 folds concentration of TNF-α than the adipocytes, in this regard, the physiologic role of microphages and adipocytes released TNF-α may be a dysregulation of cycle circle, promotion of cell proliferation and decrease apoptosis.

### *Adipose tissue and treatment outcome in breast cancer*

Emerging evidence suggests that, adipose tissue and its associated cytokine-like proteins, adipokines, particularly leptin and adiponectin, may mediate breast cancer initiation and progression (Grossmann et al., 2010; Cleary et al., 2010). For instance, whenever the carcinogen, 7,12, dimethylbenz[a] anthracene (DMBA) was administered to normal weight and diet-induced obese female Sprague-Dawley rats, cell proliferation was significantly increased particularly in mammary glands and inguinal lymphatic nodes of the rats, indicating a significant influence of obesity on breast cancer (Lautenbach et al., 2009). Furthermore, using MTT assay, Lautenbach et al. (2009), assessed effects of leptin, estrogen, and IGF-I (commonly produced by adipose tissue) on proliferation of MCF-7 cells (human breast cells), and observed a mitogenic role for these three mediators on cell proliferation, suggesting the ability of these molecules produced by adipose tissue to promote uncontrolled cell proliferation and initiate breast cancer. This means that obesity-related adipokines and mediators, leptin, IGT-1, and estrogen enhance cell proliferation in mammary gland and increase risk for breast.

Furthermore, emerging evidence suggest that adipokines may aggravate breast cancer toward more invasive and treatment resistant state. For example, a study that examined the expression of leptin and its receptor (ObR) in primary and metastatic breast cancer and noncancerous mammary epithelium, revealed that Leptin and ObR were significantly over expressed in primary and metastatic breast cancer relative to noncancerous tissues (Garofalo et al., 2006). That study included 148 primary breast cancers patients, 66 breast cancer metastases cases and 90 benign mammary lesions; and evaluated the effects of insulin, IGF-I, estradiol, and hypoxia on leptin and ObR mRNA expression (Garofalo et al., 2006). The authors clearly showed that, in primary tumors, leptin was positively correlated with ObR, and that both biomarkers (Leptin and ObR) were most abundant in grade 3 tumors (Garofalo et al., 2006). Indeed, there are sufficient published studies which demonstrate that obesity in postmenopausal women might be associated with increased breast cancer risk, development of more aggressive tumors and resistance to certain anti-breast cancer treatments; this process might be mediated by leptin acting independently or modulating other signaling pathways (Garofalo et al., 2006). Leptin may exert its activity not only through ObR, but also through crosstalk with other signaling systems. For instance, leptin affects the synthesis and/or function of estrogen receptor alpha (ERα), vascular endothelial growth factor (VEGF), and human epidermal growth factor receptor 2 (HER2) (Garofalo et al., 2006; Surmacz, 2007). HER2 is a tyrosine kinase that is amplified in 25–30% of breast tumors and it's over expression often correlates with a more aggressive, metastatic phenotype and worse prognosis (Ross and Fletcher, 1999; Yarden and Sliwkowski, 2001). In fact, data from clinical studies clearly revealed a correlation between presence of leptin and ObR (the overall association was about 93%) in both HER2-positive and HER2-negative subgroups in 59 breast cancer cases (Fiorio et al., 2008). The author demonstrated that the expression of leptin or ObR was numerically more frequent in larger and advanced metastatic (>10 mm) tumors (Fiorio et al., 2008). Further analysis in that study showed that co expression of HER2 and the leptin/ObR system might contribute to enhance HER2 activity and reduce sensitivity to anti-HER2 treatments (Fiorio et al., 2008). It is generally accepted that HER2 is a major marker of aggressive breast cancer and its important pharmaceutical target. HER2-targeted therapies with trastuzumab improve survival of patients with HER2 over expressing

metastatic breast cancer and early-stage breast cancer (Fiorio et al., 2008). However, primary or treatment-induced resistance to this drug often occurs. It appears that co expression of leptin/ObR with HER2 contributes to enhance HER2 activity and reduce sensitivity to anti-HER2 treatments in a large fraction of breast cancer patients. This may occur due to possible intratumoral ObR/HER2 interactions, and point to existence of crosstalk between HER2 and the leptin system in aggressive and treatment resistant breast cancer.

### *Sterol regulatory element-binding protein 1 (SREBP-1) pathway provides increased lipid content to drive cancer progression*

Metabolic dependency of cancer cells on cholesterol and other lipids is tightly regulated by the cholesterol homeostasis network, including (i) sterol response element-binding proteins (SREBP) (Fig. 2), master transcriptional regulators of cholesterol and fatty acid pathway genes; (ii) nuclear sterol receptors (liver X receptors, LXR), which coordinate growth with the availability of cholesterol; and (iii) lipid particle receptors, such as low-density lipid particle (LDL) receptor, providing exogenous sterol and lipids to cancer cells (Gabitova et al., 2014). In addition, activity of oncogenic receptors, such as MUC1 or EGFR, accelerates sterol uptake and biosynthesis (Gabitova et al., 2014). SREBP isoforms, three of which (SREBP-1a, 1c, and 2) are well characterized. It is now widely accepted that sterol regulatory element-binding proteins (SREBPs) is a master lipid synthetic transcription factors for cholesterol and fatty acid synthesis (Gabitova et al., 2014). SREBPs are synthesized as membrane-bound precursors with their N-terminal active portions entering the nucleus to activate target genes after proteolytic cleavage in a sterol-regulated manner (Besnard et al., 2007; Gabitova et al., 2014). This cleavage step is regulated by a putative sterol-sensing molecule, SREBP-activating protein (SCAP), that forms a complex with SREBPs and traffics between the rough endoplasmic reticulum and Golgi (Besnard et al., 2007). DNA cis-elements that SREBPs bind, originally identified as sterol-regulatory elements (SREs), now expands to a variety of SRE-like sequences and some of E-boxes, which makes SREBPs eligible to regulate a wide range of lipid genes. Animal experiments including transgenic and knockout mice suggest that three isoforms, SREBP-1a, -1c, and -2, have different roles in lipid synthesis. In differentiated tissues and organs, SREBP-1c is involved in fatty acid, whereas SREBP-2 plays a major role in regulation of cholesterol synthesis (Guo et al., 2009). SREBP-1a is expressed in growing cells, providing both cholesterol and fatty acids that are required for membrane synthesis (Besnard et al., 2007). Thus, SREBP-1 regulates de novo fatty acid biosynthesis, and controls ACLY, ACC, FASN and LDLR expression, and has been recently demonstrated to upregulate in different cancer patients, including glioblastoma (Guo et al., 2009). Glioblastoma, the most common malignant brain tumor, is among the most lethal and difficult cancers to treat. Glioblastomas (GBMs) aggressively invade the surrounding brain, making complete surgical excision impossible. Unfortunately, GBMs are also among the most radiation- and chemotherapy-resistant of all cancers. On average, GBM patients survive 12–15 months from the time of initial diagnosis (Guo et al., 2009) The epidermal growth factor receptor (EGFR), which is amplified in up to 45% of GBM patients has oncogenic activity, however, EGFR inhibitors have been ineffective in the clinic. Epidermal growth factor receptor (EGFR) mutations (EGFRvIII) and phosphoinositide 3-kinase (PI3K) hyperactivation are common in GBM, promoting tumor growth and survival, including through sterol regulatory element-binding protein 1 (SREBP-1)-dependent lipogenesis (Guo et al., 2009).

EGFR mutation together with loss of PTEN is known to activate SREBP1 and subsequently induce LDLR expression resulting in increased cholesterol influx, fulfilling the requirements of proliferating transformed cells. In addition, activation of LXR via synthetic ligands induces (i) overexpression of ABCA1 and (ii) overexpression of IDOL (inducible degrader of the LDLR), which down-regulates LDLR protein expression via ubiquitination (Moschetta, 2011; Guo et al., 2011). These molecular events drive decreased cholesterol influx and increased cholesterol efflux to cause a reduced intracellular cholesterol levels, which would block cellular proliferation and tumor growth, and inducing cell death via apoptosis (Guo et al., 2011; Gabitova et al., 2014). In addition, recent studies have uncovered potent biologic activities of certain cholesterol metabolic precursors and its oxidized derivatives, oxysterols, meiosis-activating sterols, which exert effects on trafficking and signaling of oncogenic EGFR (Guo et al., 2011). Cholesterol epoxides, the highly active products of cholesterol oxidation, are being neutralized by the distal sterol pathway enzymes, emopamyl-binding protein (EBP) and dehydrocholesterol-7 reductase (DHCR7). These recently discovered ''moonlighting'' activities of the cholesterol pathway genes and metabolites expand our understanding of the uniquely conserved roles these sterol molecules play in the regulation of cellular proliferation and in cancer.

## Can lipid biogenesis serve as a new treatment target?

Menendez et al. (2004) demonstrated in detail the role of fatty acid in tumor growth and response to treatment. Indeed, the author showed that breast cancer cells retain dependence on endogenous fatty acid synthesis and that fatty acid synthase (FAS); an anabolic-energy-storage pathway of minor importance in normal cells, that catalyses the terminal steps in the de novo biogenesis of fatty acids – play an important role in cancer progression. Presenting different experimental evidence, Menendez et al. (2004) showed that targeting lipid metabolism by FAS inhibition may be useful in treating breast cancer *in vivo*; since its pharmacological inhibition is cytotoxic and promotes apoptosis, and a pharmacological inhibition of FAS activity using natural antibiotic cerulenin [(2S,3R)-2.3-epoxy-4-oxo-7E,10E-dodecadienamide] resulted in a dose-dependent cytotoxicity, which positively paralleled the endogenous level of FAS. However a supraphysiological administration of exogenous oleic acid (OA), a omega-9 monounsaturated fatty acid synthesized from a primary-end product of FAS palmitate, significantly diminished cancer cell toxicity caused by cerulenin and pharmacological blockade of FAS activity in FAS-over expressing SK-Br3 cells resulted in apoptosis (Menendez et al., 2004). Therefore it appears that

FAS over-expression confer a survival advantage to cancer cells, which is a unique characteristics of treatment resistant state often seen in late stage of malignant and metastatic cancers. And by targeting lipid metabolism by inhibiting FASN, reverts the gain of survival advantage and promotes apoptosis and improves treatment response in cancer cells.

### *Drugging the lipid metabolism to improve treatment outcome*

In deed there are convincing evidence for a possible central role for lipid or cholestrol in cell proliferation and tumor growth. For example, rapidly growing tissues, such as the brains of newborn rats, synthesize cholesterol in a faster and more active way than tissues that demonstrate little cellular turnover, hence, alterations in the synthesis, uptake, and membrane content of cholesterol have been observed in a variety of experimental tumor models as well as in human tumors. These changes include a high rate of cholesterol biosynthesis linked to an increase in the activity of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol synthesis (Moschetta, 2011). In line with this, treatment with compactin, a very potent competitive inhibitor of HMG-CoA reductase, prevented cell proliferation (Brown and Goldstein, 1986). Interestingly, proliferating cells' requirement for increased cholesterol can also be satisfied by the up-regulation of low-density lipoprotein receptor (LDLR) and the subsequent increase of cholesterol influx (Brown and Goldstein, 1986). In most of these studies, a synchronism between increase in cholesterol synthesis and influx with the proliferative process has been observed. *In vivo* experiments provide evidence that tumor-unrelated cell proliferation, such as proliferating T cells, and regenerating liver after partial hepatectomy, as well as tumor-related hyper-proliferation status are closely associated with changes in lipid homeostasis. Strategies aimed at affecting cholesterol homeostasis are thus emerging as putative therapies against cancer.

Given that SREBP-1 (Fig. 2), regulates de novo fatty acid biosynthesis, including control of ACLY, ACC, FASN and LDLR expression, it has been shown to be upregulated in different cancer types (Moschetta, 2011). It is clear that both primary and transformed cells need cholesterol for their growth. Guo and colleagues recently unraveled the connection between epidermal growth factor receptor mutations in glioblastoma and increased cholesterol influx via sterol regulatory element-binding protein 1 and low-density lipoprotein receptor (LDLR) increase (Guo et al., 2011). They propose the activation of the liver X receptor-inducible degrader of LDLR-LDLR (IDOL) axis as a therapeutic approach to reduce intracellular cholesterol, block tumor growth, and induce cell death (Guo et al., 2011).

Furthermore, it appears that strategy toward reducing the cholesterol pool in cancer cells is challenged by the highly efficient feedback loops compensating for a blockade at a single point in the cholesterol homeostatic network.

Recently, it was shown that palmitoylation of Wnt-1 by enforced expression of ectopic FASN in immortalized human prostate epithelia cells (iPrECs) stabilized and activated β-catenin and resulted in increased oncogenicity of the iPrECs cells (Fiorentino et al., 2008). This highlights the role of endogenous fatty acid synthesis in tumor progression. For instance, in primary mouse embryonic fibroblasts and osteoblasts, palmitic acid, as well as stearic acid and myristic acid, compromised the normal response of these cells to DNA damages, thus conferring survival advantage to cells, leading to tumorigenesis (Liu et al., 2010; Wang et al., 2012). It now generally accepted that cancer cells frequently exhibit a significant increase in over expression and activity of FASN (Lupu and Menendez, 2006; Liu et al., 2010; Wang et al., 2012). Once considered an anabolic energy-storage pathway of minor importance in normal cells, the FASN concentration is normally very low in non-cancerous cells, hence, its expression is highly dependent on nutritional conditions in lipogenic tissues ((Medes et al., 1953; Lupu and Menendez, 2006; Shah et al., 2006; Vazquez-Martin et al., 2008). FASN-catalyzed endogenous FA biosynthesis in liver and adipose tissue is stimulated by a high carbohydrate diet, whereas it is suppressed by the presence of small amounts of FAs in the diet and by fasting (Kridel et al., 2007; Vazquez-Martin et al., 2007). Currently, FASN is slowly emerging as a marker for diagnosis and prognosis of human cancers. Recent studies showed that FASN is an oncogene and inhibition of FASN effectively and selectively kill cancer cells (Vazquez-Martin et al., 2008). With recent publications of the FASN crystal structure and the new development of FASN inhibitors, targeting FASN opens a new window of opportunity for metabolically combating cancers. With malignant progression to androgen independence, prostate cancer cells develop resistance to apoptosis and exhibit a variety of gene expression changes, including increased fatty acid synthase (FASN) expression (Vazquez-Martin et al., 2008; Liu et al., 2010). Increased FASN expression has been shown to correlate with poor prognosis, and correspondingly, the FASN gene has been proposed as a therapeutic target (Shah et al., 2006; Liu et al., 2010; Wang et al., 2012).

Accordingly, pharmacological inhibitors of FASN activity preferentially kill cancer cells and retard the growth of tumors in xenograft models (Liu et al., 2010; Wang et al., 2012; Cheng et al., 2014). Although few of these FASN blockers are expected to be selective for FASN, the relevance of FASN as a target for anti-neoplastic intervention has been confirmed by RNAi-knockdown of FASN (Vazquez-Martin et al., 2008). For example, RNAi-mediated down-regulation of FASN expression resulted in a major decrease in the synthesis of triglycerides and phospholipids and induced marked morphological changes, including a reduction in cell volume, a loss of cell–cell contacts, and the formation of spider-like extrusions, and silencing of the FASN gene by RNAi significantly inhibited LNCaP cell growth and ultimately resulted in induction of apoptosis (De Schrijver et al., 2003). In addition, Menendez et al. (2005) also reported that FAS pathway as a potent molecular target to enhance the efficacy of taxanes-based chemotherapy in human breast cancer. Because FASN is an androgen regulated gene in the prostate, therefore treatment with antihormone drug, for example, dutasteride a novel dual inhibitor of the 5 alpha-reductase enzymes currently in use for treatment of benign prostate hyperplasia (BPH) – inhibits FASN mRNA, protein expression and enzymatic activity in prostate cancer cells and controlled tumor growth (Schmidt et al., 2007).

In treating breast cancer, FASN inhibitors, amentoflavone was isolated from *Selaginella tamariscina*, a traditional oriental

medicine that has been used to treat cancer for many years, was found to significantly inhibit *in vitro* enzymatic activity of FASN, and decrease fatty acid synthesis by the reduction of [(3) H] acetyl-CoA incorporation into lipids in FASN-over expressed SK-BR-3 human breast cancer cells (Lee et al., 2009). A decrease in breast cancer cell growth was observed in SK-BR-3 cells at 12 and 24 h post treatment with amentoflavone, followed by a dramatic suppression after 48 h (Lee et al., 2009).

Elucidating the mechanisms underlying resistance to the human epidermal growth factor receptor 2 (HER2)-targeted antibody trastuzumab (Tzb; Herceptin) is a major challenge that is beginning to be addressed. This dilemma is becoming increasingly important as recent studies strongly support a role for Tzb in the adjuvant setting for HER2-overexpressing early-stage breast cancers. A study has demonstrated that pharmacological and RNA interference treatment induced inhibition of tumor-associated FASN (Oncogenic antigen-519), a key metabolic enzyme catalyzing the synthesis of long-chain saturated fatty acids, drastically down-regulates HER2 expression in human breast cancer cells bearing HER2 gene amplification (Vazquez-Martin et al., 2007). Given that FASN blockade was found to suppress HER2 over expression by attenuating the promoter activity of the HER2 gene (Vazquez-Martin et al., 2007), it appears that this mechanism of action may represent a valuable strategy in breast cancers that have progressed while under Tzb. Evidence showed that both HER2 mRNA and HER2 protein over-expression, in Tzb-resistant breast cancer models, were entirely suppressed following pharmacological blockade of FASN activity (Vazquez-Martin et al., 2007; Cheng et al., 2014). Moreover, while Tzb was still able to reduce HER2 protein expression by approximately 20%, a small-compound specifically inhibiting FASN activity, the C75 and Tzb co-exposure synergistically down-regulated HER2 protein levels by >85% (Vazquez-Martin et al., 2007; Cheng et al., 2014). The nature of the interaction between Tzb and C75 in Tzb-resistant SKBR3/Tzb100 cells was also found to be strongly synergistic when analyzing the extent of apoptotic cell death; this means that FASN inhibition acts on HER2 gene expression via reduction of its transcription rate, and transcriptional suppression of HER2 expression using FASN blockers may represent a new molecular strategy in the management of Tzb-resistant breast cancer disease (Vazquez-Martin et al., 2007). These data provide evidence that FASN inhibitors induced breast cancer apoptosis through blockade of fatty acid synthesis.

In addition, LXRs are putative pharmacological targets in atherosclerosis because they are able to decrease intracellular cholesterol by up-regulation of cholesterol efflux (via induction of the target gene ABCA1) and down-regulation of cholesterol influx [via induction of the target gene IDOL (inducible degrader of LDLR), which blocks LDLR via ubiquitination] (Moschetta, 2011). From the preceding paragraphs, it has been clarified that LXR transcriptional activities relates to driving and sustaining fatty acid synthesis. In fact a recent works of Guo and colleagues (2011) clearly indicated that LXR synthetic ligands are able to decrease cell growth and induce significant tumor cell death *in vivo*; this phenomenon occurred by repression of LDLR protein expression via IDOL activation and induction of ABCA1 (Guo et al., 2011). This lipogenic role of LXR, especially in the liver, leads to systemic hypertriglyceridemia, which today represents a limitation for a putative LXR-targeting therapeutic strategy for cancer treatment. Also, one cannot exclude that fatty acid synthase activity might be increased by LXR for example in glioblastoma cell, whose proliferation is indeed additionally blocked when LXR ligands are administered together with fatty acid synthesis inhibitors (Guo et al., 2011). Overall, this work clearly indicate opportunities in designing novel therapeutic approach for better treatment response in cancer therapy

In conclusion, fatty acids synthesized by FASN in cancer cells are not only used for cellular membrane construction, but also involved in the production of lipid signaling molecules, anchorage of membrane proteins, and modulate cellular responses to anticancer drugs (Vazquez-Martin et al., 2007; Cheng et al., 2014). We have shown that inflammatory mediators played important role in tumorigenesis and malignant cancer progression in both solid and hematologic cancers (Omabe and Kenneth, 2014). We have presented some details regarding the role of adipocyte derived inflammatory molecules and the SREBP-1 in cancer progression. In addition, the role of fatty acid metabolism in cancer progression and treatment is well clarified. It is possible that the increased de novo synthesis of palmitate by FASN over-expression plays an important role in mediating FASN effect in a number of cancers including breast and prostate cancer. Inhibition of this pathway may provide important opportunity for successful treatment, however it appears FASN inhibition only target the endogenous pathway, and allows the exogenous route and inflammatory agonist to escape. This means that targeting other molecules responsible for exogenous fatty acid metabolism may promote better treatment response.

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