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Lipid Metabolism in Mammary Neoplasia and Potential Therapeutic Targets

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ABSTRACT

Benign and malignant mammary neoplasias are common in women and domestic dogs and cats. Dogs and cats share (more so than rodent models) many of the risk factors, including increased incidence with age, for spontaneous mammary neoplasia. Dogs are affected by both benign and malignant types of tumors while in cats malignant neoplasms are the most common. Human mammary neoplasia is characterized by altered lipid metabolism. For example, the expression of fatty acid synthase (named oncogene antigen, OA 519) was identified as a marker for aggressive human breast cancer more than two decades ago. Considering lipogenesis is enhanced in breast and other types of cancer, many have suggested on the need to develop inhibitors of selected steps along the lipogenetic pathway as targets for chemotherapy. Several such agents are at different phases of development. The objective of this review is to provide an overview of lipid synthesis in normal and neoplastic mammary glands and potential chemotherapeutic targets affecting lipid metabolism. We conclude by suggesting the use of dogs and cats as animal models may hasten the development of therapeutic approaches.

Keywords: *lipid metabolism, mammary cancer, fatty acid synthesis, lipogenesis*

INTRODUCTION

Benign and malignant mammary neoplasias are common in women and female companion animals. In USA alone, each year, 290,000 new cases of breast cancer are diagnosed and about 40,000 women and men die of the disease. It is the second leading cause of death (after lung cancer) in women [1]. Among domestic animals, mammary neoplasia is most prevalent in dogs and cats. The incidence of mammary neoplasia in dogs can be as high as 200 cases/100,000 per year [2], rate similar to humans [1]. The age-adjusted incidence a rate simlilar to "humans" of mammary neoplasia in female and male dogs is 3x and 16x that of women and men, respectively [3]. In dogs, most of the neoplasia (~55%) is benign while in cats, similar to human, most of the pathology (>80%) involves invasive tumors [4,5].

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The occurrence of spontaneous mammary neoplasia increases as the animal ages, and other similarities in the pathophysiology of the tumors between dogs and cats, and humans have led to the consideration of dogs and cats as valuable models (more appropriate than rodents, where the mammary tumors are induced) to study human breast cancer and develop therapeutic approaches [6-8].

One of the emerging hallmarks of cancer are alteration in metabolism [9-11]. Compared to quiescent tissues, neoplastic cells are characterized by an increased rate of glycolysis. There are also marked changes in lipid metabolism due to increased demand for cell components such as membranes. In most cancer cells, both lipid catabolism and anabolism are upregulated [12,13]. The need for membrane phospholipid bilayer is fulfilled mainly from de novo lipogenesis (DNL) and not from plasma or dietary lipids [9]. In fact, fatty acid synthase (FAS) a key enzyme in DNL has been identified in the blood as a marker for invasive breast cancer in women [14,15]. Lipid metabolism related genes are also significantly upregulated in canine mammary tumors that are aggressive [8]. Thus, targeting

DNL has the potential to interfere with ability of neoplastic cells to proliferate by disabling their membrane generating ability. Many *in vitro* studies have shown that DNL inhibitors are toxic to cancer cells, demonstrating their potential therapeutic effects.

Fatty Acid and Lipid Synthesis by Normal and Neoplastic Tissues

Details on lipids and related substrate metabolic pathways, in either normal or neoplastic cells have been presented elsewhere [16-19]. Intracellular lipids may originate either from circulating (dietary) fatty acids (FA) or (with the exception of essential ones) from FA synthesized within the cell. In neoplastic cells, FA originating from DNL but not dietary (circulating) FA serve as building blocks of lipids [9] (Figure 1). The synthesis of FA starts with the carboxylation of acetyl CoA. The latter may originate from mitochondrial citrate that is shuttled to cytosol and then broken down to acetyl CoA and oxaloacetate, or from a ligase reaction between acetate and CoA (Figure 1).

The carboxylation of acetyl CoA produces a four-carbon compound, malonyl CoA, and is catalyzed by acetyl CoA carboxylase (ACC), a rate-limiting enzyme. Subsequent elongation and/or desaturation reactions lead to the formation of saturated and unsaturated fatty acids. Fatty acid synthase catalyzes some of the elongation reactions. The fatty acids are then esterified with glycerol-phosphate to form mono-, di- or triglycerides; the diphosphoglycerides make up the bulk of the phospholipid bilayer of biological membranes. The glycerol may originate from dihydroxyacetone phosphate of glycolysis or direct phosphorylation of glycerol. Additionally, the production of phospholipids without glycerol backbone (e.g. sphingosines) increases in breast cancer [20,21].

Thus, glycolysis, pentose phosphate pathways, Krebs (TCA) cycle and other pathways provide precursors for DNL. Thus, multiple therapeutic targets are available to affect DNL.

Hexokinase is the first enzyme involved in the glycolysis pathway and among key enzymes that can affect lipid metabolism in the normal and neoplastic cancer cells. There are four subtypes. Type 1 hexokinase produces glucose-6-phosphate for glycolysis and is also responsible for coordinating glycolysis with the TCA cycle. Types 2 and 3 Hexokinase are responsible for producing glucose-6-phosphate for lipid synthesis.

Pyruvate dehydrogenase kinase (PDH) down regulates the PDH, which is responsible for converting pyruvate to acetyl CoA. Monoacylglycerol lipase is responsible for converting monoacylglycerides to free fatty acids and glycerol.

Carnitine palmitoyl transferase (CPT)-1 facilitates transport of fatty acids into mitochondria for beta-oxidation.

ATP Citrate Lyase (ACL) cleaves citrate to acetyl-CoA and oxaloacetate in the cytoplasm and is often upregulated in cancer [10].

Acetyl CoA Carboxylase (ACC) is responsible for the carboxylation of acetyl CoA to produce malonyl CoA. Of the two forms, ACCα is highly expressed in the cytoplasm of lipogenic cells such as mammary glands and adipose tissue. ACC β is mainly present within skeletal muscle and in the heart where it is responsible for regulating fatty acid oxidation within these tissues. The liver contains significant amount of both types of ACC.

Fatty Acid Synthase (FAS) catalyzes the conversion of Malonyl-CoA to long-chain fatty acids. The elongation utilizes NADPH as a reducing agent. In normal tissues, de novo lipid synthesis is generally suppressed making the need for FAS nonexistent. De novo lipogenesis is generally elevated in cancer cells because of the increased need for energy and lipids for cellular proliferation which cannot be met by glycolytic activity or dietary (circulating fatty acids) alone (Figure 1). FAS expression is upregulated in several types of cancer including those of prostate, ovarian, colon, and lung cancers [10,22].

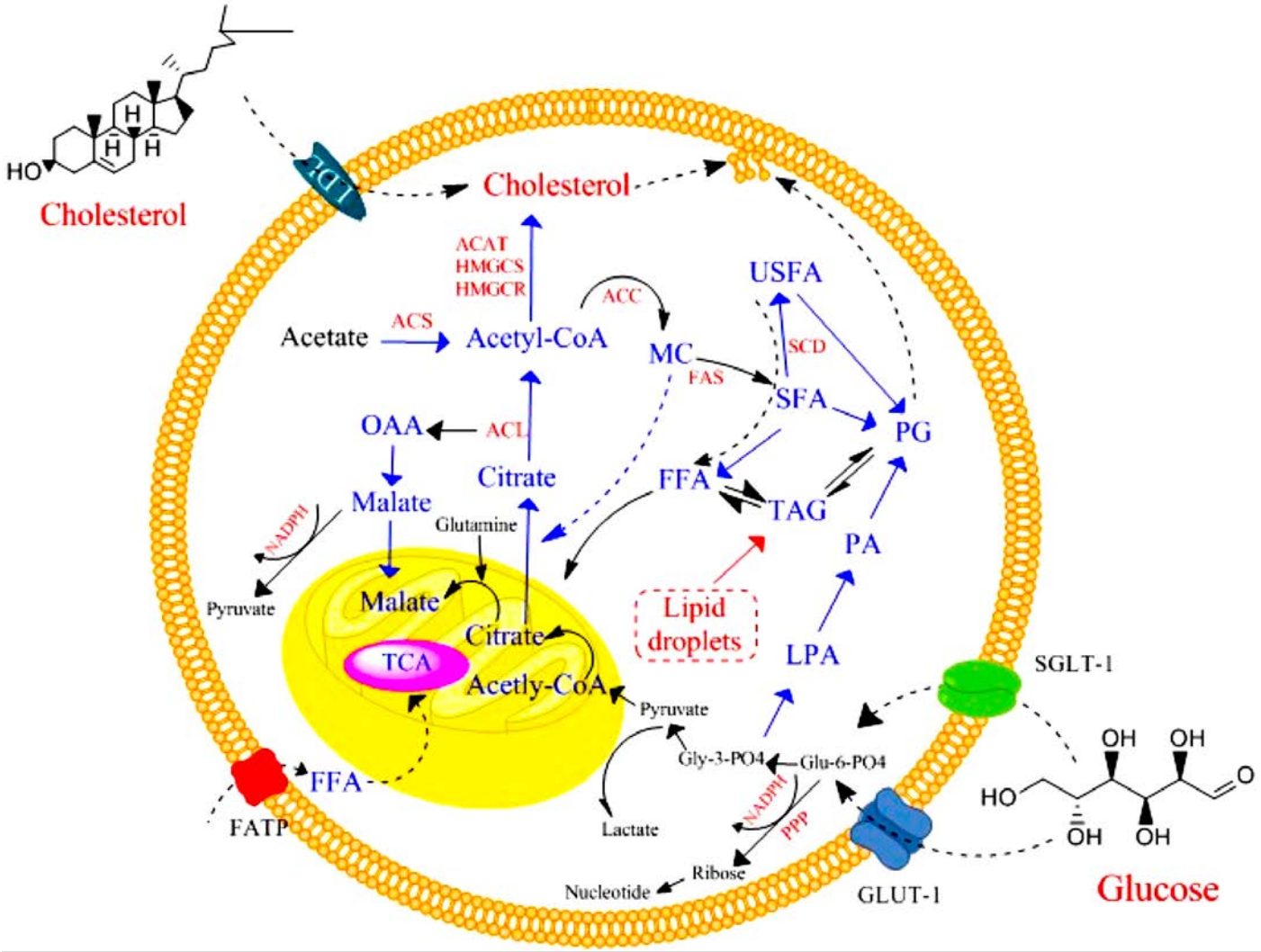
Besides FAS, cancer cells overexpress **choline kinase,** which is responsible for synthesizing important membrane phospholipids- phosphatidylcholine and sphingomyelin**.** [20,21,23]. Mammary tumor cells also overexpress other key regulators of lipid metabolism such as sterol regulatory element-binding protein (SREBP) [19]. The up regulation of several enzymes in lipid metabolism of cancer cells makes these enzymes excellent targets for treatment. Enzyme inhibitors, depending on their target(s), have the potential to induce apoptosis in cancer cells or to prevent cancer cells from effectively maintaining their energy and molecular requirements to continue proliferation. [24].

Lipid Metabolism as Target for Cancer Therapy

Enzyme inhibitors have the potential to revolutionize cancer treatment; hence, treatments targeting lipid metabolism have become a current hot topic of research. Unfortunately, with the constant need for lipid metabolism in the body, some of these inhibitors have the potential to affect normal bodily functions as well as preventing growth of tumors. [25]. The mammary gland is also physiologically active in lipogenesis; hence sorting out normal vs. cancer-related effects on enzyme/metabolic activity is very crucial. Nevertheless, many agents have shown promising efficacy both *in vitro* and in xenografts of breast cancer cells. Table 1 shows partial list of the treatments targeting some enzymes in lipid metabolism those are at different stages of clinical development.

For example, the cerulenin derivative, C75, was effective when tested on MCF-7 breast cancer cell culture and xenografts; when given to xenografted nude mice tumor size was <12.5% in C75-treated animals as compared to controls [26]. Several of them such as Orlistat [27,28], hydroxycitrate and metformin have been approved for weight loss and to treat diabetes but not for cancer therapy. The use of animal models, especially dogs and cats, could hasten the development of safer mammary cancer

Figure 1: A summary of lipid metabolism in normal and neoplastic mammalian cells



Proliferating cells have high demand for cell components such as membranes, the major components of which are phospholipids (phophoglycerates, PG). Cholesterol is also an important membrane component. Under the action of GPAT (Glycerol-3-phosphate acyltransferase), Glycerol-3-phosphate (Gly-3-PO4), a product of glycolysis, gives rise to lisophosphatidic acid (LPA) and then phosphatidic acid (PA). Fatty acids (FA, saturated or unsaturated- SFA; USFA) and PA esterify to form PGs. One source of the FA is de novo synthesis starting with the carboxylation of Acetyl-CoA (AC) to form malonyl-CoA (MC), which is subsequently elongated and/or subjected desaturation processes; MC also inhibits the shuttling of FA into the mitochondria for oxidation. Alternatively, FA may originate as free FA (FFA) from plasma lipoproteins or the hydrolysis of intracellular triacyl glycerols (TAG) of lipid droplets (LD). FATP (fatty acid transport proteins) facilitate uptake of FFA by cells. Similarly, uptake of LDL-bound Chol via LDL receptors is another source of cholesterol. Due to increased demand, stored or plasma supply of FFA and cholesterol to the neoplastic machinery is unlikely to fulfill the requirements for proliferation; hence, de novo synthesis of FA and cholesterol from AC likely plays a major role. AC could be produced from citrate [Cit, originating from amino acids like glutamine, Glut, and cataplerosis from mitochondrial tricarboxylic acid (TCA) cycle], or synthesized in the cytosol from acetate. Oxaloacetate (OAA), a cleavage product of Cit becomes anaplerotic to TCA by being converted to malate (Mal). Mal can also form pyruvate (Pyr) with the generation of NADPH, which along with NADPH from the pentose phosphate pathway (PPP) is used as a reducing agent during elongation of FA and cholesterol synthesis.

Enzymes: GPAT (Glycerol-3-phosphate acyltransferase), ACL (ATP citrate lyase), ACS (Acetyl CoA synthase), ACC * (Acetyl CoA Carboxylase), FAS (Fatty acid synthase), SCD (Stearoyl-CoA Desaturase), ACAT (Acyl-CoA cholesteryl acyltransferase), HMGCS (Hydroxymethylglutaryl Coenzyme A Synthase), HMGCR* (HMG-CoA reductase).*

*Enzymes marked with * are considered rate-limiting.*

chemotherapeutic strategies.

Table 1: Some therapeutic agents targeting lipid metabolism tested for their effects on mammary neoplasia

Hexokinase
2-deoxyglucose [34]
Oroxylin A [35]
Pyruvate Dehydrogenase Kinase
Dichloroacetate [36]
Mitochondrial respiratory chain complex I
Metformin [37]
ATP Citrate Lyase
Radiciol [38]
Hydroxycitrate [39]
SB-24990 [40]
Acetyl-CoA Carboxylase
Soraphen A [41]
Ethylhexanoic acid [42]
Chlorophenoxy-methylpropionic acid [42]
Fatty Acid Synthase
Amentoflavone [43]
Orlistat [28]
Cerulenin [44]
C75 [26, 44]
Mevalonate Pathway (cholesterol synthesis)
Statins [40]
Farnesyl transferase inhibitors [40]
Methyl-β-cyclodextrin [45]
Sphingomyelin pathway [20]
C_6-ceramide [46]
Sphingosine kinase inhibitors (FTY270) [47]
Phosphocholine synthesis
MN58b [21]

Concluding Remarks

To meet their energy and cellular component needs, neoplastic cells primarily rely on DNL. There are numerous potential therapeutic targets that can be utilized to affect lipid metabolism. Some of the currently available cancer chemotherapies (e.g. antagonists of growth factors such as tyrosine kinase inhibitors) exert their effects downstream, in part, by interfering with lipid synthesis [29]. Specific targeting of cholesterol synthesis or uptake by tumor cells is also likely to reduce fluidity of membranes and hence the metastatic ability of tumor cells. The overall goal includes inhibiting DNL and enhancing lipid oxidation that will have effects similar to caloric restriction, which has already been shown to be beneficial in the prevention and treatment of different cancer [30,31]. Alternative approaches could also target uptake of glucose and fatty acid by tumor cells.

Although there is strong evidence for increased expression of several lipogenic genes in mammary neoplasia, the gland is also physiologically active in large scale lipid synthesis during lactation and pseudopregnancy. For example, mammary ACC1 mRNA expression increased by two-folds while that of stearoyl-CoA desaturase (SCD) and SREBP1 increased up to 40 times, during lactation in mice and domestic cows [32,33]. A major challenge, as with other cancer chemotherapies, is how to selectively target the pathways in neoplastic cells without compromising normal mammary tissue which is also endowed with DNL capacities.

The complexity of the network of pathways influencing lipid metabolism require that we fully understand how an agent affects normal functions of the specific tissue and organism. Unraveling ideal targets in a specific cancer type is crucial to utilize the breadth of knowledge available to us and those developing in the future. Thus, in order to target the DNL pathway for cancer therapy, an understanding of key-differences and similarities between normal and neoplastic DNL is necessary. Additionally, the potential of these agents to synergize with the conventional chemo-, radiation, or molecularly targeted therapies needs to be explored. A rational combination regimen that targets for example lipid metabolism and growth factor signaling pathways may exhibit a better therapeutic index and clinical outcome. The use of dogs and cats, which spontaneously develop mammary carcinoma in a manner similar to humans, should be helpful in characterizing the physiological vs. neoplastic up regulation of lipogenic genes and hasten the development of therapeutic targets for mammary neoplasia.

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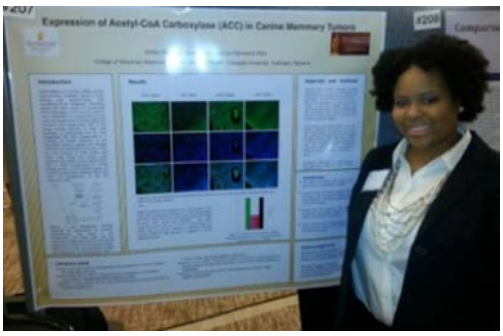

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