REVIEW ARTICLE

Lipid Metabolism—An Aberrant Shift in Cancer: A Narrative Review

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ABSTRACT

Cancer is a multifactorial disease characterized by uncoordinated proliferation and growth of tumor cells. To survive, cancer cell undergoes various metabolic reprogramming by changes in the pathways. The role of glucose and amino acid metabolism in cancer has been studied extensively. However, lipid metabolism and its role in cancer are less explored. The concept of lipid metabolism has gained attention of researchers to discover its importance in understating the need of lipids for tumor cell growth and survival through various mechanisms to help us for improvising therapeutic strategies. Hence, in this review, we have highlighted the pivotal role of lipid metabolism in normal cell and cancer cell with illustrations.

Keywords: Acetyl-coenzyme A carboxylase, Adenosine triphosphate-citrate lyase, Cancer cell, Fatty acid synthase, Lipid metabolism, Stearoyl-coenzyme A desaturase.

INTRODUCTION

Several reactions take place in a mammalian cell simultaneously in a well-organized and integrated manner. The entire range of chemical reactions taking place in the cell is called metabolism. Series of enzymatic reactions takes place to produce specific products that hold the metabolic pathway. Metabolic pathway can be broadly divided into two main categories as catabolism and anabolism.[1] Catabolism is a process of degradation in which the complex molecules are broken and are converted down to the simpler ones with the liberation of energy [adenosine triphosphate (ATP)]; on the contrary, anabolism is a biosynthetic reaction that involves the formation of complex molecules from simple precursors with the consumption of energy ATP. Both the catabolic and anabolic pathways are nonreversible and function independently.[1,2]

Among all the metabolites, lipids are considered as the building blocks of many cells and organelles. Many of the lipids are formed from fatty acids fatty acid synthase (FASN) which get transformed into diacylglycerides and triacylglycerides (TAGs) through glycerol phosphate pathway, in the presence of glycerol-3-phosphate, a glycolytic intermediate to produce glycerol. These TAGs play an essential role in the signaling pathways and function as second messengers and hormones.[3] Triacylglycerides store energy in the form of lipid droplets (LDs).[2] Lipid droplets are universally preserved dynamic organelles that store and mobilize fatty acids and other lipid species for their multiple cellular roles.[4] Besides, the products of this pathway can be changed into different phosphoglycerides. Along with phosphoglycerides, phosphatidylcholine (PC), phosphatidylethanolamine, phosphatidylglycerol, and phosphatidylserine contribute to the membrane constituents. Further, sterols mainly cholesterol and cholesterol-esters are essential for membrane functioning.[5]

The fatty acids are derived either from carbohydrates or synthesized *de novo*. The requirements of the lipids to the tissues are fulfilled by uptake of free fatty acids and lipoproteins like low-density lipoprotein (LDL). The biosynthesis of the fatty acids is restricted to a subgroup of tissues.[6-8]

Metabolic reprogramming is considered as a major hallmark of cancer that provides cancer cells not only the energy but also vital metabolites to maintain their aberrant survival and growth. Metabolism generates free oxygen radicals, which contribute to oncogenic mutations. Carbohydrates, lipids, and proteins play a foremost role in metabolism.[3] Regulation of lipids is essential in malignancy, as they play a vital role in formation of membrane constituents of tumor cells as well as they act as a source for energy for biophysical and signaling pathways performing the process of tumorogeneis.[3,7]

Hence, this review attempts to summarize the concept of lipid metabolism in normal cells and draw comparison with the lipid metabolism in cancer cells (tumor cells).

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We brief about the key enzymes involved in the process of lipid metabolism before discussing its role in cancer development.

ROLE OF KEY ENZYMES IN NORMAL CELLS

Adenosine Triphosphate-citrate Lyase

The ATP-citrate lyase (ACLY) is a cytosolic enzyme that bridges glucose metabolism and fatty acid metabolism. The conversion of mitochondrial-derived citrate into acetyl-coenzyme A (CoA) takes place by ACLY. Acetyl-CoA is one of the main predecessors for both fatty acid and mevalonate synthesis pathways. Acetyl-CoA is an essential backbone for the biosynthesis of fatty acids and cholesterol endogenously. In addition to the above, acetyl-CoA plays an important role in isoprenoid-based protein modifications and acetylation reaction that modifies the proteins, such as histone acetylation.[9,10] Many studies have shown the upregulation of ACLY enzyme in cancer cells, and that its inhibition suppresses the proliferation of certain types of tumor cells (Fig. 1A).[9]

Acetyl-CoA Carboxylase

It is a biotin-dependent enzyme that catalyzes the irreversible carboxylation of acetyl-CoA (ACC) and forms malonyl-CoA. It is the most highly regulated enzyme in the fatty acid synthesis pathway. Acetyl-CoA carboxylase is positively regulated by citrate and glutamate.[7] In the human genome, ACC has two subtypes: ACC1 and ACC2. ACC1 is highly enriched in lipogenic tissues and ACC2 takes place in oxidative tissues. Both ACC1 and ACC2 are found to play different metabolic roles, as both are found to exist in different tissues.[5] Acetyl-CoA carboxylase regulates the regulatory step in the synthesis of fatty acids and it is controlled by balance between the active and less active forms of ACC involving reversible phosphorylation.[10,11] Acetyl-CoA carboxylase, a key enzyme in fatty acid synthesis, has been thought to play an important role in the development of breast and ovarian cancer by interacting with BRACA1c by satisfying the lipid demands of the tumor cells.

The role of ACC in cancer cells still needs to be discovered. Acetyl-CoA carboxylase activity might be controlled by promoting ACC phosphorylation. However, knockdown of ACC1 induces apoptosis in prostate cancer and breast cancer as well.[10]

Fatty Acid Synthase

Fatty acid synthase is a significant biosynthetic enzyme involved in the process of lipogenesis and in the production of long-chain fatty acids from acetyl-CoA and malonyl-CoA.[12] Acetyl-CoA and malonyl-CoA are then combined to the acyl-carrier protein domain of the multifunctional enzyme FASN. Synthesis of palmitic acid, which is a basic saturated fatty acid, is a result of continuous condensations of acetyl groups at 16th carbon position. Increased fatty acid synthesis occurs because overexpression of FASN has been detected in human cancers, such as breast and ovarian cancers.[10] Normal cells have low levels of expression and activity of FASN, which is tightly regulated by diet, hormones, and growth factors.[10,13]
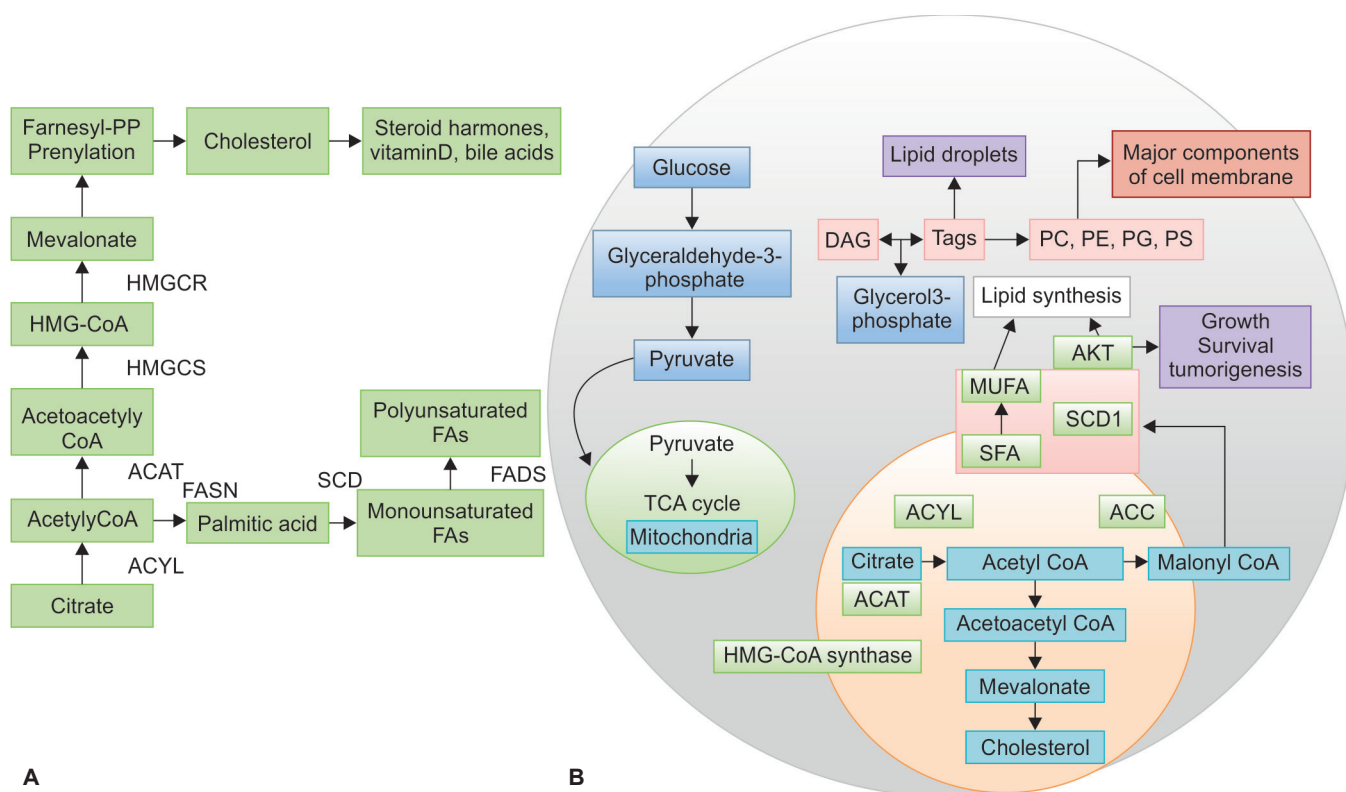
Stearoyl-CoA Desaturase

One of the key regulators for fatty acid composition of cellular lipids is stearoyl-CoA desaturase (SCD), also known as fatty acyl-CoA delta-9 desaturases, predominantly located in endoplasmic reticulum (ER).[14] Monounsaturated fatty acids (MUFA) synthesis is generated by introduction of a double bond at the delta-9 position of palmitic and stearic acid. Stearoyl-CoA desaturase has several isotypes (forms) varying in their localization and roles. These are SCD1 and SCD5 (Fig. 2).[14] The SCD1 is found in almost all tissues with a major expression in liver, whereas SCD5 expression is restricted to pancreas and brain.[14]

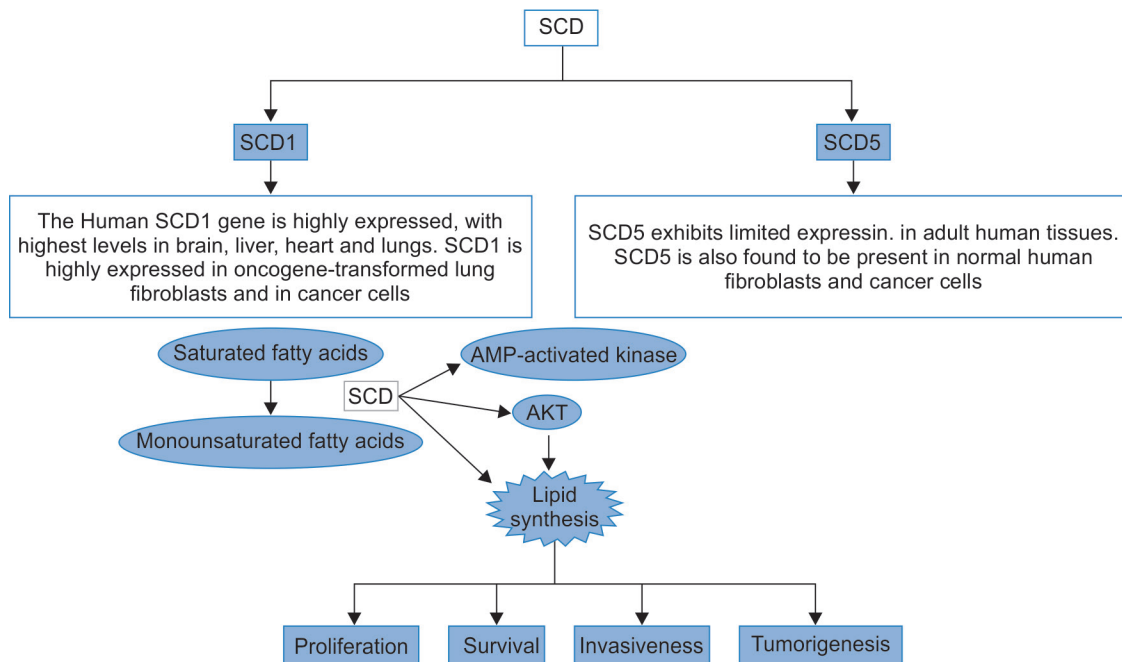## REPROGRAMMING OF LIPID METABOLISM IN CANCER

One of the most common features of cancer cells is the intense reprogramming of the metabolic pathways. Lipid metabolism pathway being one among them gets altered in rapidly proliferating tumor cells. An increase in glucose uptake and the use of aerobic glycolysis, termed as the Warburg effect, is the most prominent metabolic alterations found in cancer (Fig. 1B).[15]

The most important metabolic hallmark of tumor cell is increased *de novo* synthesis of lipids by extensive production of FAS and phospholipids. Aberrant lipid metabolism affects various cellular processes, including cell growth, proliferation, differentiation, and motility (Fig. 3). These changes can affect the synthesis of membranes by hindering the availability of structural lipids.[4] Many studies have shown that the intense proliferation of tumor cells have a strong affinity toward lipids and cholesterol, and desires of these tumor cells will be met either by increasing the exogenous lipid lipoproteins or increased endogenous synthesis through lipogenesis and cholesterol synthesis. These exogenous lipids are stored as lipoproteins in cancer cells, and these are considered as hallmarks of cancer aggressiveness.[4]

Cancer cells are thought to upregulate *de novo* fatty acid synthesis frequently to satisfy their demands for lipids for the self-sustainability. Fatty acids require

Figs 1A and B: Role of lipid metabolism in normal mammalian cell (A), and in cancer cell (B), HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A; HMGCS: Hydroxymethylglutaryl-CoA synthase; HMGCR: 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; FADS: Fatty acid desaturases; ACAT: Acetyl-CoA-acetyltransferase; Farnesyl PP: Farnesyl pyrophosphate
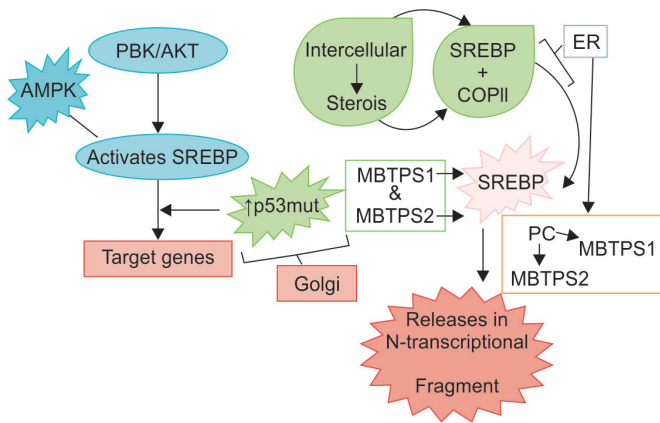

Fig. 2: Signaling of SCD in cancer

activation to enter the bioactive pool via fatty acyl-CoA synthetases. Once the fatty acid reaches activation pool, it gets esterified with glycerol, generating triacylglycerol (stored in the LDs). During depletion of nutrient energy, lipids provide energy to the cancer cells.[9]

ACTIVATION OF THE ONCOGENIC PATHWAYS STIMULATES LIPID SYNTHESIS

Metabolic reprogramming in cancer cell is associated with mutations of protooncogenes and tumor-suppressor genes which sequentially play a role in the development

Fig. 3: Schematic presentation of SREBP in cancer

and growth of cancer. One such aberrant metabolism is abnormal lipid synthesis resulting in increased synthesis of lipids.[14]

To prevent lipotoxicity and membrane dysfunction, synthesis of lipid has to be controlled in a synchronized manner. Enzymes involved in fatty acid biosynthesis are regulated by the sterol-regulatory element binding proteins (SREBPs). Sterol-regulatory element binding proteins, a family of transcription factors, play a vital role in maintaining the homeostasis of lipid in cells.[14] Sterol-regulatory element binding proteins are helix–loop–helix 125 kDa protein, which exist in membranous part of ER through inactive precursors, and these will bond to SREBP cleavage-activating protein (SCAP).[5] Sterol-regulatory element binding proteins exist in three isoforms: SREBP1 is the most abundant form. It regulates fatty acid, triacylglycerol, and phospholipid synthesis. SREBP2 regulates cholesterol generation or controls the expression of the cholesterol synthesis genes. SREBP1c regulates fatty acid synthesis.[5,16]

The activity of SREBPs is tightly regulated by the concentration of intercellular sterols as shown in Figure 3. When the concentration of sterols is limited, the SREBP/SCAP complex gets associated with cytoplasmic coat protein complex (COPII) (a type of specific protein complex that transports protein from rough ER to the golgi apparatus) coated vesicles and gets translocated to the golgi. Cleavage of SREBP takes place with the help of two membrane-bound proteases at site-1 and site-2 protease (MBTPS1 and MBTPS2 in golgi). During this process, proteolytic cleavage releases N-transcriptionally active fragment. Nuclear translocation can occur due to the release of MBTPS1 and MBTPS2 to the ER membrane which in turn is stimulated by the decrease in the levels of the membrane phospholipid PC.[5,16,17]

Studies have shown that the variations in the expression of various genes involved in cholesterol and fatty acid biosynthesis are activated by protein kinase b (Akt) that mediates the growth factor signaling effects through the

phosphatidylinositol-3-kinase (PI3K) pathway. The PI3K/Akt/protein kinase B signaling pathway is frequently activated in human cancer. In the regulation of proteolysis, the activity of SREBPs transcription factor is modulated by its interaction with transcriptional coactivators. Sterol-regulatory element binding proteins can also be associated with the activator recruited cofactor/mediator complex to activate specific target genes.[5,16]

The SREBP1 and SREBP2 are overexpressed in number of cancers, such as breast cancer and hepatocellular cancer. Sterol-regulatory element binding proteins is activated by aberrant epidermal growth factor receptor in human glioblastoma multiforme.[12] Aberrant activation of SREBP and induction of expression of its target genes, such as FASN and LDL-receptor are thought to be upregulated in tumor cells of breast cancer, ovarian and prostate cancer. The transcription of the androgen-receptor gene is regulated by the SREBP which promotes proliferation, migration, and invasion in prostate cancer, and also the expression of SREBPs vary during the progression of cancer.[5,17]

Mutant tumor protein p53 along with SREBP are the promoters of genes within the mevalonate pathway and increase their expression; this hyperactivation disrupts tissue architecture and promotes the formation of breast cancer, placing SREBP-dependent lipogenesis at the core of the transformation process.[18] Studying glioblastoma, demonstrated that epidermal growth factor-receptor mutations and hyperactivation of PI3K promote tumor growth and survival through stimulation of SREBP1 activity.[5]

ROLE OF FASN IN CANCER

Fatty acid synthase plays a role of key enzyme when involved in neoplastic lipogenesis.[12] The major role of FASN in development of cancer was well documented since two decades, when the oncogenic antigen-519, a molecular marker, was identified in breast cancer patients. Acetyl-CoA, malonyl-CoA, and Nicotinamide adenine dinucleotide phosphate hydrogen are utilized by FASN as reducing equivalents.[18]

Increased fatty acid synthesis is caused by multiple mechanisms, including increased expression of lipogenic enzymes. Fatty acid synthase overexpression is observed in human cancers. Transcriptional regulation of FASN gene is an important mechanism of FASN overexpression. The FASN expression is regulated by growth factors and the steroid hormones[18] (Fig. 4).

Downstream of the receptors, the PI3K-AKT and mitogen activity protein kinase (MAPK) are the candidate signaling pathways and promote FASN expression through SREBPs1c. Mutual regulation between FASN and the growth factor-dependent signaling suggests Human
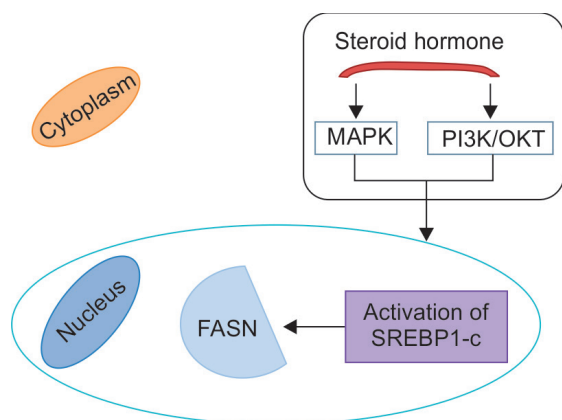
Fig. 4: Signaling of FASN in cancer

epidermal growth factor receptor-2 induces FASN expression through the downstream PI3K signaling pathway. Fatty acid synthase expression is said to be controlled by not only the SREBP1c but also by other transcription factors, such as p53 family proteins and the lipogenesis-related nuclear protein. The extracellular tumor microenvironmental stresses also play an important role in the FASN expression. Hypoxia and low pH stress induce the FASN expression in cancer cells. SREBP1, the major transcriptional regulator of the FASN gene, is upregulated in cancer through phosphorylation of Akt.[17-19]

During the synthesis of lipids through FASN activity, it is important to pay an attention for the lipid rafts. Lipid rafts can be defined as membranous lipid domains which are rich in cholesterol and sphingolipid that contain several signaling and transport proteins. Caveolae are the type of lipid raft that are rich in the caveolin protein family. Studies have shown that the expression of Caveolin-1 encoding gene has been altered in cancers, such as colon, breast, esophageal, squamous cell, and prostate cancer. The studies have also shown that FASN and Caveolin-1 can be coexpressed in the malignant cells.[2,12,18]

Researchers have found significant correlation between the expression of FASN and prognosis in patients with cancer. They have suggested that increased expression of FASN cases could have poorer prognosis with lesser survival rate and high recurrence rates in patients with cancers of various organs, such as breast, kidney, ovary, colorectal, lung, head and neck, prostate renal melanoma, and other malignancies, such as nephroblastoma and melanoma.[16]

ROLE OF SCD IN CANCER

Stearoyl-CoA desaturase-1 plays a supporting role in many human cancers including lung, breast, prostate, and clear cell carcinoma.[14] The presence of increased amount of MUFA in most of the glycolipids is a common finding in various cancer cells.[3]

Stearoyl-CoA desaturase-1 uses either exogenous or endogenous source for the production of MUFA from the initiating substrates of saturated fatty acid (SFA). Recently, the studies have shown that abnormal increase in the levels of MUFA is thought to be a metabolic hallmark of carcinogenesis, mainly the endogenously synthesized MUFA. The abundance of MUFA in the cancer cells is due to enhanced activity of SCD1. Experimental studies done in cellular models suggest that the gradual reduction in SCD1 expression induced in a tumor cell is directly proportional to the deficiency in the content of cellular MUFA. Thus, SCD1 is, indeed, found to be the main regulator for the homeostasis of MUFA.[3,12,20]

Enhanced activity of SCD1 is an important factor in ascertaining the disturbances in the metabolic pathways that promote the carcinogenesis. Abnormal increase in the level of SCD1 is the best-characterized SCD isoform that is commonly found in neoplastic cells. This provides an early evidence that SCD enzyme might be responsible for the onset and progression of cancer.[21] As the levels of MUFA in cancer cells vary, there is an opposing alteration in the relative content of polyunsaturated fatty acids. The main function of SCD1 in mammalian cell is to regulate the lipid synthesis by directing the rate of biosynthesis of major fatty acids, such as triacylglycerol and cholesterol esters which are usually found in lesser amount in cancer cells. This suggests that SCD1 is a key regulator for lipogenic programming in cancer. SCD1 also has role in determining the balance between MUFA and SFA, which are the most available substrate pools for acylations in cancer. Stearoyl-CoA desaturase-1 may contribute to drive lipogenesis by enhancing fatty acid synthesis through various mechanisms involving the storage of chemically active ACC, an important enzyme that takes part in the formation of malonyl-CoA in the fatty acid biosynthetic pathway. Studies have shown that increased levels of SCD1 could conquer the activity of adenosine monophosphate-activated protein kinase (AMPK) that mainly aims ACC for inactivation via hyperphosphorylation, through conversion of SFA into MUFA. In addition, SCD1 controls catalysis of ACC by continuous removal of saturated acyl-CoA, which is the most powerful allosteric inhibitors of ACC. For the progrowth and survival of cancer cell, SCD1 is an essential for the activation of Akt pathway that controls the activation of many lipogenic enzymes.[3,14]

The increased amount of MUFA by SCD1 is not just a metabolic byproduct but also has an influence in balancing the synthesis of lipids as well as in survival signaling pathways which will eventually modify the main mechanism in cancer.[3,22]

CONCLUSION

Cancers are diverse set of lesions with hidden gene line alterations and reprogramming of the various metabolic pathways including lipid metabolism. Lipid metabolism with its complex pathways, regulatory mechanisms, and enzymes having various isoforms coupling with each other could possess different cellular localization or tissue distribution, stimulating the oncogenic pathway. Therefore, this review provides extensive knowledge of aberrancy of lipid metabolism which could help us to analyze and target the specific therapy for cancer.

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