Lipid metabolism in cancer: A systematic review

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Abstract:
Preclinical studies and clinical trials have emphasized the decisive role of lipid metabolism in tumor proliferation and metastasis. This systematic review aimed to explore the existing literature to evaluate the role and significance of the genes and pathways most commonly involved in the regulation of lipid metabolism in cancer. The literature search was performed as per Preferred Reporting Items for Systematic Reviews and Meta-analyses. Approximately 2396 research articles were initially selected, of which 215 were identified as potentially relevant for abstract review. Upon further scrutiny, 62 of the 215 studies were reviews, seminars, or presentations, and 44 were original study articles and were thus included in the systematic review. The predominant gene involved in lipid metabolism in cancer was stearoyl-coenzyme A desaturase 1 (SCD1), followed by fatty acid synthase (FASN). The pathway most commonly involved in lipid metabolism in cancer was the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signaling pathway, followed by the mitogen activated protein kinase (MAPK) pathway. SCD1 and FASN play significant roles in the initiation and progression of cancer and represent attractive targets for potentially effective anti-cancer treatment strategies. The regulation of cancer metabolism by the Akt kinases will be an interesting topic of future study.

Keywords:
Akt, fatty acid synthase, lipid metabolism, oral cancer, PI3K, signaling pathways, stearoyl-coenzyme A desaturase

Introduction
Cancer is the leading cause of death in economically developed countries.[1] Total cancer deaths are projected to increase from 7.1 million in 2002 to 11.5 million in 2030.[2] The burden of cancer is alarming in economically flourishing countries due to population growth and the adoption of lifestyle choices associated with an increased risk of cancer, such as smoking, physical inactivity, and processed diets.[3] Cancers arise from the accumulation of genetic and epigenetic changes and abnormalities in cancer-associated signaling pathways.[4] Metabolic reprogramming, a major hallmark of cancer, provides cancer cells with both energy and various metabolites vital for maintaining their aberrant survival and growth. Metabolism generates oxygen radicals, which contribute to oncogenic mutations.[5] Lipids are among these vital metabolites; lipid metabolism is a multistep process involving several key enzymes and is suggested to generate the building blocks of many cells and organelles. Moreover, lipids play important roles as second messengers and hormones.[6] Lipid metabolism is regulated by multiple signaling pathways and generates a variety of bioactive lipid molecules. An increase in lipid metabolism is a remarkable feature of cancer metabolism, deregulation of or abnormalities in these signaling pathways might result in abnormal cell proliferation and growth. Physiological processes such as cell growth, proliferation, differentiation,
survival, apoptosis, inflammation, motility, membrane homeostasis, response to chemotherapy, and drug resistance are regulated by lipid metabolism. Understanding the genes and pathways most commonly involved in lipid metabolism in cancer could help provide evidence for elucidating the mechanisms of cancer cell death and potentially help in the discovery of potential cancer therapeutic targets. This systematic review aimed to study the existing literature to evaluate the role and significance of the genes and pathways most commonly involved in the regulation of lipid metabolism in cancer.

The following key question was constructed according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines: “Do the genes and pathways associated with lipid metabolism play a significant role in cancer progression?”

**Materials and Methods**

This systematic review was written according to PRISMA. Prospero databases were searched for any registered protocol on similar topic, no title related to or resembling the current title was found.

**Inclusion criteria**

The articles included in the study were full-length, English language articles that focused on basic research on genes and associated signaling pathways involved in lipid metabolism in cancer.

**Exclusion criteria**

The exclusion criteria were articles on topics other than lipid metabolism as an etiological factor in cancer; studies that lacked proper validation of their results; articles other than original research, such as reviews, editorial letters, books, and abstracts; and studies with insufficient data.

**Data sources and search strategy for literature on lipid metabolism in cancer**

Databases such as PubMed, Google Scholar, Scopus, EBSCO, E-Journals and Science Direct were searched using key words such as “genes in lipid metabolism of cancer,” “pathways in lipid metabolism of cancer” and “biomarkers in lipid metabolism of cancer.” PubMed searches were also performed for references cited in review articles on lipid metabolism in cancer. Articles published until October 2017 were included. References of the selected articles were again screened for additional relevant studies that could have gone undetected during the electronic search.

**Data collection**

The data collection was performed in two phases. Initially, the articles were evaluated as a whole, and we listed the various genes and their role in cancer. The second phase included an evaluation of the different techniques used and an assessment of the validation of the results in each article. The overall data collection form was used to obtain the following information from the individual articles: Authors, Journal in which the article was published, Year of publication, Research focus, Methodologies employed, Results obtained, Conclusions and Future scope of research in the given field.

**Synthesis of results**

The results of the individual studies were then summarized, and the various genes involved in lipid metabolism in cancer were entered on a list. Data on the same genes were grouped and analyzed. Individual points of interest across the selected studies were summarized.

**Results**

**Search results**

Upon conducting a search with the abovementioned key words, 2396 search results were identified. However, these results included seminars, conference presentations, letters to editors, short communications, journal publications, and books. Among these 2396 results, 80 articles were identified as potentially relevant. The title and abstract of these articles were reviewed. 62 articles that fit the inclusion criteria were selected and further reviewed by two researchers for reliability. In cases of disagreement, a third reviewer was consulted. Among the 62 articles, 18 were excluded for the following reasons: articles on topics other than lipid metabolism as an etiological factor in cancer; studies that lacked proper validation of their results; articles other than original research, such as reviews, editorial letters, books, and abstracts; studies with insufficient data; and articles published before 2009. A total of 44 articles were selected for the systematic review by the reviewers [Figure 1].

**Study results**

A total of 44 articles were selected by the reviewers. The selected original research articles focus on lipid metabolism in cancer progression, as shown in Table 1.

A total of 38 genes were found to be involved in lipid metabolism in cancer progression, as shown in Table 2. The most commonly involved gene was stearoyl-coenzyme A desaturase 1 (SCD1), followed by fatty acid synthase (FASN), which was identified in 7 studies. Fatty acid binding protein 4 (FABP4) was described in 5 studies.

Table 3 depicts the most common metabolic pathways implicated in cancer progression. Eight metabolic
signaling pathways responsible for cancer progression were identified. Among these, the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway was the most commonly implicated in cancer development and progression,[8,12,14,19,26,27,32,41,46,47] followed by the mitogen activated protein kinase (MAPK) and mechanistic target of rapamycin (mTOR) pathways (MAPK pathway,[7,22,32,47] and mTOR pathway:[12,19,27,33]).

Table 4 shows the various lipogenic inhibitors that could be used as therapeutic drugs to suppress the activity of a gene product in the tumor. The most commonly reported inhibitor was TOFA (5 tetradecyl oxy 2 furoic acid).[42,50,51]

**Discussion**

Cancer cells usually display aberrant cellular metabolism that directly contributes to tumorigenicity and malignancy. The main abnormality is aerobic glycolysis. Metabolic alterations are highly associated with mutations in oncogenes and tumor suppressor genes that play an important role in cancer development and progression. Increased lipid synthesis is one of the most significant metabolic aberrations in cancer cells. Lipids are considered the building blocks of cell membranes during cell proliferation and also function as signaling molecules. Recent discoveries on the impact of indispensable lipid enzymes in cancer progression have extended our knowledge of lipid metabolism and its impact on tumor etiology.[13] The activation of oncogenes and the loss of tumor suppressor genes contribute to metabolic reprogramming in cancer, which subsequently results in enhanced uptake of nutrients to further supply biosynthetic pathways.[53] It is important to identify the genes involved in lipid metabolism, as they will provide numerous avenues for confirming the impact of targeting the associated pathways in cancer.

**The most commonly involved genes in lipid metabolism in cancer**

The most commonly reported gene involved in lipid metabolism in cancer was SCD1, followed by FASN and FABP4.

**Stearoyl-coenzyme A desaturase 1**

SCDs are mainly localized in the endoplasmic reticulum and are also known as fatty acyl-CoA delta-9 desaturases. SCD1 is a crucial regulator of the fatty acid composition of cellular lipids. To generate monounsaturated fatty acids (MUFA), SCD1 catalyzes the formation of a double bond at the ninth positions of palmitic acid and stearic acid.[80] In human tissue, there are two SCDs, SCD1, and SCD5. SCD1 expression is sensitive to fatty acids and carbohydrates, and it is regulated by hormones and various growth factors. SCD5, another variant of SCD, was recently found to be present in higher amounts in the human brain, pancreas and embryonic tissue; however, its biological role remains uncharacterized.[53] SCD1 is known to play a significant role in many human cancers, such as breast, lung, hepatocellular, prostate, and clear cell carcinoma, depicted in Figure 2. Several cancer cells and tissues have abnormal high levels of Monounsaturated fatty acids (MUFA) in major glycerolipids. High SCD1 levels act as a chief cofactor in creating metabolic disturbances or aberrancies that favor oncogenic processes. The presence of abnormally increased levels of SCD1 in various types of cancer cells provides initial evidence that this enzyme may be functionally connected to the onset and progression of cancer.[53] TNM stage, tumor grade, and lymphatic metastasis have been positively correlated with SCD1

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Figure 1: Selection of articles represented by Preferred Reporting Items for Systematic Reviews and Meta-analyses flowchart

Figure 2: Regulation of stearoyl-coenzyme A desaturase 1 as a key regulator of lipid biosynthesis in cancer cells
Table 1: Summary of the selected articles

| Author                  | Year | Biomarkers/genes involved | Cell lines and tissue samples | Methodology                                                                 | Conclusion                                                                 |
|-------------------------|------|----------------------------|-------------------------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Rohena-Rivera et al.[8] | 2017 | PLCG2, RAC1, GATA3, DTX1, CTR9, TCF4, CPT2, FABP4, PLIN2 | PC3 and 22RV1 46 tumor tissue samples | Cell culture, Scratch wound healing assay, Invasion assay, Orthotopic mouse model, Tissue collection and processing, Hematoxylin and eosin staining, IHC and IF, PCR analysis, Microarray analysis, Real-time PCR validation | *IL-5 increases tumor volume as a consequence of inflammation and lipid mobilization* |
| Qian et al.[9]          | 2017 | THBS2, INHBB, BGN         | 562 colorectal cancer samples | Genomic analysis 4                                                              | Lipid metabolism might play critical roles in the carcinogenesis and liver metastasis. THBS2, INHBB and BGN are prognostic markers and potential therapeutic targets for CRC |
| Li et al.[10]           | 2017 | ATOH8, DMRT2, TBX15, ZNF367 | 621 breast cancer samples 208 controls | Microarray data collection and preprocessing, Differential gene expression analysis, Gene set enrichment analysis, Transcription factor analysis | The tissue-specific gene expression profile in breast cancer will require careful consideration in theoretical research and validation in future clinical practice |
| Che et al.[12]          | 2017 | FASN                      | FASN mice AlbCre: FASN cell line | Hydrodynamic injection and mouse monitoring, qRT-PCR IHC | The studies demonstrated the importance of FASN and its ability to regulate the *de novo* lipogenic metabolic cascade in hepatocarcinogenesis |
| Wang et al.[15]         | 2016 | SCD1                      | 359 ccRCC patient samples     | IHC                                                                           | SCD1 was found to be overexpressed in ccRCC tissues at a high rate |
| Luo et al.[13]          | 2017 | B7-H3                     | A549, H446                    | RT-PCR, Western blotting, RNAi-mediated gene silencing, Immunocytfluorescence IHC, Oil red O staining, Total triglycerides | B7-H3 modulates lipogenesis via the SREBP1/FASN signaling pathway in lung cancer cells |
| Gualia-Esteruelas et al.[14] | 2017 | FABP4, FABP5, CD36       | MCF-7, MDA-MB-231             | Western blotting, IF microscopy, Cell proliferation, *In vitro* wound healing assay, Viability analysis, Cytotoxicity | eFABP4 plays a key role in tumor proliferation and activates the expression of fatty acid transport proteins in MCF-7 breast cancer cells |
| Blomme et al.[11]       | 2017 | Myoferlin                 | MDA-MB-231, MDA-MB-468, BT-474, SK-BR-3, MCF-7, ZR-75-1 | MRI of xenografts, Histology, IF, IHC, Western blot, Gas chromatography, Nuclear magnetic resonance, Isolation of mitochondria, Apoptosis assay, Oxygen consumption | Myoferlin is an important oncogene that plays a notable role in tumor progression |
| Author          | Year | Biomarkers/genes involved                     | Cell lines and tissue samples | Methodology                                           | Conclusion                                                                 |
|-----------------|------|-----------------------------------------------|-------------------------------|------------------------------------------------------|---------------------------------------------------------------------------|
| Gaggini et al.  | 2017 | FNDC5/Irisin, SCD-1, SREBF-1, NOTCH1, IL-6, TNF-alpha | 36 subjects                  | Real-time PCR, Plasma lipid profile analysis, ELISA  | The induction of FNDC5/Irisin expression in the liver might play a role in a potential therapeutic strategy for the treatment of metabolic diseases and carcinogenesis |
| Christensen et al. | 2016 | SNHG16                                        | 314 colorectal adenomas, 292 adjacent normal colon mucosa samples | RNA isolation and sequencing, Microarrays, RT-qPCR, Polysome analysis, Cell fractionation and viability analyses, Ingenuity pathway analysis, HuR immunoprecipitation, Motif enrichment analysis, AGO-CLIP target analysis | SNHG16 upregulation is an early event in CRC                                |
| Lee et al.      | 2014 | FABP4                                         | 27 SCC samples resected from the tongue | IHC, Cell culture and cell growth assay, RNAi approach, Western blot analysis | FABP4 is a potential target for the treatment of oral SCC                    |
| von Roemeling et al. | 2015 | SCD1                                          | RWV366T, KU625T, A498, Caki2, and ACHN, K347N, K360N, K355N, K365N and K366N mutations | Cell lines, DNA microarray, Growth assays, RNA isolation and quantitative PCR, Western blot analysis, IHC, IF, Lentivirus infection, Cell death analysis by flow cytometry, In vivo analysis | SCD1 is a novel oncogenic factor specifically required for tumor cell viability in ATC and may serve as a prognostic biomarker |
| Nanjappa et al. | 2015 | SCD in OKF6/TERT1                             | OKF6/TERT1, FaDu and CAL27    | Chewing tobacco extract, Cell culture, Treatment of OKF6/TERT1 cells with chewing tobacco siRNA transfection, Cell proliferation assays, Sample preparation, Chromatography, LC-MS/MS analysis, Western blotting, Cell invasion assays, Colony formation assays | Overexpression of SCD in response to chewing tobacco mediated oncogenic transformation in oral cells |
| Chen et al.     | 2016 | SCD1                                          | Lovo, Colo205, and SKOV3 45 colorectal cancer samples | Cell culture, RNA isolation and qRT-PCR, Lipid extraction and analysis, Proliferation assay, Western blot assay, Flow cytometry assay | High SCD1 levels were found in colorectal cancer and could be used as a predictive biomarker and therapeutic target in this disease |
| Author                | Year | Biomarkers/genes involved | Cell lines and tissue samples | Methodology                                                                 | Conclusion                                                                 |
|----------------------|------|---------------------------|------------------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Angelucci et al.     | 2015 | SCD1                      | MCF-7, MDA-MB-231            | Breast cancer cell lines Cocultures qRT-PCR Western blot analysis siRNA Wound healing assay | CAFs play a role in promoting tumor cell migration, which could help in designing therapeutic strategies |
| Rahimi et al.        | 2015 | SCD1                      | HiPSC9, HepG2                | Cell culture SCD1 inhibition Production of hepatic markers Gene expression analysis Lipid analysis | The requirement for SCD1 activity in the functional differentiation of hepatocytes may have relevance for human liver disease and metabolic dysregulation |
| Kim et al.           | 2015 | FABP4 and FASN            | 476 breast cancer samples MCF-7, MDA-MB-453, MDA-MB-435S, MDA-MB-231, and MDA-MB-468 | Cell culture Western blot analysis Construction of tissue microarrays IHC FISH analysis | Lipid metabolism-related proteins are differentially expressed in different types of breast cancer, which may aid in the development of novel chemotherapeutic agents |
| Wang et al.          | 2015 | BCAT1                     | OVCAR3, SKOV3, OV-90, OV2008, TOV-112 and TOV-21 | Cell culture Tissue microarrays shRNA Functional assays Gene expression profiling and data analysis Western blotting Metabolomics analysis | BCAT1 was identified as a novel EOC biomarker and a putative EOC therapeutic target |
| Belkaid et al.       | 2015 | SCD1                      | MCF-7, T47D, MCF-10A        | Fatty acid analysis RNA extraction qPCR Immunocytochemistry Western blot | SCD1 is a crucial player in the mitogenic effect of estrogen, supporting the premise that SCD-1 is a therapeutic target in breast cancer |
| Sangeetha et al.     | 2015 | FASN                      | WERI-RB1 Y79 25 RB samples  | FASN siRNA transfection Gene expression analysis by qRT-PCR Western blot analysis FASN ELISA Microarray Cell viability assessment by MTT Annexin assay Scratch assay | FASN is correlated with tumor invasion and is a promising target in the clinical management of RB |
| Yang et al.          | 2015 | VEGF, p53, and Ki67       | 82 patients with CRC        | Sample collection Gas-liquid chromatography (PUFA composition in tissues) ELISA IHC | The metabolism of PUFAs may play an important role in the evolution of inflammation-driven tumorigenesis in CRC |

Contd...
| Author          | Year | Biomarkers/genes involved     | Cell lines and tissue samples | Methodology                                                                 | Conclusion                                                                 |
|-----------------|------|-----------------------------|-------------------------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Daniëls et al.  | 2014 | FASN, ACACA, ACYL, ACSS2 and HMGCR | HOP62, HepG2 and PC3M         | Cell culture, Proliferation assay, 3D cell culture, ATP assay, Immunoblotting assay, RNA isolation and qRT-PCR, Apoptosis assay, Nanofluidic proteomic analysis, Lipid synthesis | A lipid-reduced growth environment differentially attenuates the proliferation of various cancer cell lines |
| Li et al.       | 2013 | SCD1                        | SCD1 mice FVB/N mice          | IHC, Oil red O staining, Western blotting, qRT-PCR                          | Inhibition of SCD activity in human cancer cells will help achieve sufficient tumor growth inhibition |
| von Roemeling et al. | 2015 | SCD1                        | ccRCC cell lines              | Growth assays, Lentivirus, Transfections, Luciferase assays, RNA isolation, Quantitative PCR, Gene array expression analysis, Western blot analysis, IHC, In vivo analysis | Increased SCD1 expression supports ccRCC viability, and SCD1 is a novel molecular target for the treatment of advanced or metastatic disease |
| Bansal et al.   | 2014 | SCD1                        | HepG2, Hep3B, and PLC/PLF/5 64 HCC tissue samples, 10 normal tissue samples | Cell lines, tissues and reagents, Immunoblot analysis, IHC, siRNA and transfection, Cell viability, Cell proliferation | SREBP-1 is a key transcription factor that regulates FA synthesis by upregulating the expression of various lipogenic enzymes, including SCD. The expression of SCD was enhanced in human HCC. |
| Ide et al.      | 2013 | SCD1 upregulated            | 29 samples of diagnosed cases of breast cancer | Imaging mass spectrometry analysis, Lipid analysis, IHC                     | The high SCD1 expression in cancerous areas indicated that this enzyme partially mediates the production of MUFA-PC. |
| Noto et al.     | 2013 | SCD1                        | Pe d/10, Pe e/10, Pe o/11, Pe s/11, Pe p/11, NCI-H460 | ALDH activity assay, Western blot analysis, Real time RT-PCR analysis, Apoptosis assay, MTT assay, Spheroid-forming assay, siRNA transfection, Morphometric analysis, Transmission electron microscopy, IF, In vivo studies, IHC | The data strongly suggest that SCD1 may be a promising target for lung cancer |
| Holder et al.   | 2013 | SCD1                        | 250 patients with stage I-III breast cancer | Fine needle aspirate, Reverse phase protein array | SCD1 is critical for malignant progression and has potential as a therapeutic target |
| Author          | Year | Biomarkers/genes involved | Cell lines and tissue samples | Methodology                                                                 | Conclusion                                                                                                                                                                                                 |
|-----------------|------|---------------------------|-------------------------------|-----------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mason et al.    | 2012 | SCD1                      | HCT116, DU145, and MIA-PaCa2  | Fatty acid preparation Mass spectrometry analysis siRNA transfection Small molecule inhibitor therapy HCT116 xenograft | The data show an unambiguous link between fatty acid synthesis and cancer cell survival, and the authors stated that SCD1 is a key target in this pathway                                                                 |
| Nieva et al.    | 2012 | SREBP-1c                   | MDA-MB-435, MDA-MB-468, MDA-MB-321, SKBR3, MCF7 and MCF10 | Cell culture Immunocytochemistry and cell labeling Raman spectroscopy | The lipid phenotype of cells is indicative of their proclivity to mesenchymal transition related to aggressive behavior and metastatic spread                                                                 |
| Liu et al.      | 2012 | FABP4                     | MDA-MB-435S and BT20 176 breast cancer tissues and 10 normal tissues | Gene profiling Tissue microarray Immunostaining | FABP7 was identified as an adverse prognostic factor that is predominantly expressed in triple-negative breast cancer                                                                 |
| Wang et al.     | 2012 | ATP citrate lyase          | A2780                         | qRT-PCR Western blotting RNAi MTT assay | ACL is an adverse prognostic factor that is overexpressed in ovarian cancer                                                                                                                                 |
| Hilvo et al.    | 2012 | SCD1                      | 257 breast cancer tissue samples | Lipidomic analyses of breast cancer tissue IHC Functional experiments in breast cancer cells | Gene expression related to lipid metabolism in tumor cells could reveal potential therapeutic targets                                                                                                                                 |
| Calvisi et al.  | 2011 | FASN, ACAC, ACYL, ME, SCD1, HMGCR, MVK, SQS | 68 HCCs Wild-type FVB/N mice | Histopathological analysis qRT-PCR Immunoblotting IHC | Inhibitors of lipogenic signaling, including those that inhibit the AKT pathway, might be useful as therapeutics for patients with liver cancer                                                                                                                                 |
| Roongta et al.  | 2011 | SCD1                      | A549, H1299, and FaDu          | Western blot analysis Flow cytometry analysis MTS analysis IHC In vivo pharmacological analysis | SCD is a potentially viable target for the design of novel anticancer agents                                                                                                                                 |
| Jin et al.      | 2010 | FASN                      | SKBR3 and BT474                | Cell culture Mass spectrometry Kinase assay Immunoprecipitation and Western blot analysis IF analysis siRNA transfection FASN enzymatic activity assay Tumor cell invasion assay | FASN phosphorylation by HER2 plays an important role in breast cancer progression                                                                                                                                 |
| Hess et al.     | 2010 | SCD1                      | AG01518, H460 human lung adenocarcinoma | Crystal violet assay Flow cytometry assay DNA fragmentation assay | SCD1 controls cell cycle progression and apoptosis                                                                                                                                 |
| Monaco et al.   | 2010 | ACSL4                     | MCF-7, MDA-MB-231, MD-MB-415, SKBR3, BT-20 | Analysis of ACSL4 protein expression Quantitation of cell number siRNA-mediated knockdown of ACSL4 | Increased ACSL4 expression was seen in breast cancer and prostate cancer ACSL4 expression is indicative of steroid hormone-independent growth |
expression in various studies. SCD1 knockdown inhibits various tumor cells that depend on the reduction of synthesized fatty acids and regulates the AKT-mTOR pathway. Thus, SCD1 could be a prognostic indicator of cancer severity. A study by von Roemeling et al. found that SCD1 may be a prognostic biomarker. SCD1 expression has been shown to be upregulated in numerous neoplastic lesions, including adenocarcinoma and gastric, breast, prostate, ovarian, and colon cancer. Thus, SCD1 has been suggested as a molecular target in several tumor types, including clear cell renal carcinoma, and may be a prognostic biomarker.

| Author          | Year | Biomarkers/genes involved | Cell lines and tissue samples | Methodology                                                                 | Conclusion                                                                                                                                                                                                 |
|-----------------|------|---------------------------|-------------------------------|----------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Scaglia et al.  | 2009 | SCD1                      | A549 human lung adenocarcinoma cancer cells | Cell culture Stable knockdown of SCD1 gene expression Immunoblotting Lipid extraction Determination of SCD1 activity Metabolic labeling Lipid analysis Cell proliferation analysis Colony analysis Apoptosis analysis Analysis of tumor formation | The authors postulate that the specific inhibition of SCD1 activity in cancer cells decreases the MUFA/SFA ratio in cell membrane lipids, leading to the inactivation of Akt signaling and impaired lipogenesis |
| Yamashita et al.| 2009 | SREBP1                    | 54 HCC samples                | Tissue samples SAGE Analysis of signaling networks RT-PCR RNA targeting SREBP1 Cell proliferation assay Soft agar assay Tunnel assay Annexin V staining Focus assay Western blotting IHC | SREBP1 activates lipogenesis pathways and may serve as a good biological prognostic biomarker and a target for therapeutic intervention |
| Agostini et al. | 2014 | FAS                       | SCC-4, -9, -15 and-25         | Cell culture Proliferation curves Immunocytochemistry Mitotic index Protein extraction and Western blotting RNA purification and RT-PCR | FAS is expressed by human oral SCC cell lines and is a potential chemotherapeutic target in oral SCC |
| Moore et al.    | 2005 | SCD1                      | Microdissection               | cDNA microarray hybridization QPCR Northern analysis IHC | Loss of SCD expression is a frequent event in prostate adenocarcinoma |
| Falvella et al. | 2002 | SCD1                      | 179 male mice                | mRNA subtraction Northern blot analysis Nucleotide sequence analysis Genetic linkage mapping | The SCD1 gene was overexpressed in the normal liver of mouse and rat strains genetically susceptible to hepatocarcinogenesis. SCD1 overexpression was also detected in a subset of rodent hepatocellular tumors |

IHC: Immunohistochemistry, IF: Immunofluorescence, PCR: Polymerase chain reaction, qRT-PCR: Quantitative reverse transcription polymerase chain reaction, MUFA: Monounsaturated fatty acids, PC: Phosphatidylcholine, SFA: Saturated fatty acids, SCC: squamous cell carcinoma, HCC: Hepatocellular carcinoma, CRC: Colorectal cancer, CMRI: Magnetic resonance imaging, ELISA: Enzyme-linked immunosorbent assay, ATC: Anaplastic thyroid carcinoma, LC-Ms: Liquid chromatography-mass spectrometry, PUFAs: Polyunsaturated fatty acids, ATP: Adenosine Triphosphate, ACL: ATP Citrate Lyase, MTS: [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2(4-sulfophenyl)-2H-tetrazolium]
### Table 2: Genes involved in lipid metabolism of cancer

| Abbreviation | Gene name | Observed change | Co-relation | Author and year | Type of neoplasm |
|--------------|-----------|----------------|-------------|-----------------|------------------|
| SCD1         | Steraoyl-CoA desaturase | Upregulated Downregulated | Associated with cell proliferation and malignant transformation | Ide *et al*., 2013  Noto *et al*., 2013  Nanjappa *et al*., 2015  Christina *et al*., 2013  Ashley *et al*., 2012  Wang *et al*., 2016  Christina *et al*., 2015  Chen *et al*., 2015  Angelucci *et al*., 2015  Moore *et al*., 2004  Roongta *et al*., 2011  Hess D *et al*., 2010  Manson *et al*., 2012  Bansal *et al*., 2013  Rahimi *et al*., 2015  Favella *et al*., 2012  Hilvo *et al*., 2011  Li *et al*., 2013  Scaglia *et al*., 2009  Belkaid *et al*., 2015 | Hepatocellular carcinoma  Lung cancer  Clear cell renal cell carcinoma  Anaplastic thyroid carcinoma  Prostate cancer  Breast cancer  Breast cancer  Human lung adenocarcinomas |
| FABP4        | Fatty acid binding proteins | Upregulated | Associated with increased cell proliferation | Lee *et al*., 2015  Liu *et al*., 2012 | Oral squamous cell carcinoma |
| FASN         | Fatty acid synthase | Upregulated | Associated with cell proliferation and malignant transformation | Agostini *et al*., 2004  Jin *et al*., 2010  Sangeetha *et al*., 2015  Che *et al*., 2017  Sangeetha *et al*., 2015 | Oral squamous cell carcinoma  Breast cancer  Retinoblastoma, hepatocellular carcinoma |
| SREBP-1C     | Stearoyl regulatory elementary binding protein 1-c | Upregulated | Associated with high metastatic spread | Nieva *et al*., 2012 | Breast cancer |
| FABP4, FASN  | Fatty acid binding protein, fatty acid synthase | Upregulated | Associated with cell proliferation | Kim *et al*., 2015 | Breast cancer |
| ACLY         | ATP citrate lyase | Upregulated | Associated with cell progression | Wang *et al*., 2012 | Ovarian cancer |
| FASN, ACAC, ACYL, ME, SCD1, HMGCR, MVK, SQS | Fatty acid synthase, Acetyl Co-enzyme A carboxylase ATP citrate lyase, 3-hydroxy-3-methylglutaryl-CoA-reductase, Malic enzyme, Stearoyl - CoA desaturase, Mevalonate kinase, Stearoyl regulatory binding protein 1 and 2 branched chain amino-acid transaminase 1 | Upregulated | Associated with cell proliferation, cell migration | Calvisi *et al*., 2011 | Hepatocellular cancer |
| BCAT1        | Branched chain amino-acid transaminase 1 | Upregulated | Associated with increase cell proliferation, migration and inhibited cell cycle progression | Wang *et al*., 2015 | Ovarian cancer |
Table 2: Contd...

| Abbreviation | Gene name                                                                 | Observed change | Co-relation                                      | Author and year | Type of neoplasm       |
|--------------|----------------------------------------------------------------------------|-----------------|-------------------------------------------------|-----------------|------------------------|
| SREBP1       | Stearoyl regulatory element binding protein 1                              | Upregulated     | Associated with cell proliferation               | Yamashita et al., 2009 | Hepatocellular carcinoma |
| B7-H3        |                                                                             | Upregulated     | Associated with tumor progression, metastasis   | Luo et al., 2016   | Lung cancer             |
| FABP4        | Fatty acid binding protein-4                                              | Upregulated     | Associated with tumor progression               | Gualta-Esteruelas et al., 2016 | Breast cancer          |
| CD36         | Fatty acid binding protein-5                                              | Upregulated     | Associated with tumor progression               |                  |                        |
| THBS2        | Thrombospondin                                                           | Upregulated     | Associated with tumor metastasis               | Qian et al., 2017  | Colorectal cancer       |
| INHBB        | Inhibin, beta B                                                           | Upregulated     | Associated with cell adhesion, proliferation, differentiation and metastasis processes | Li et al., 2017   | Breast cancer           |
| BGN          | Biglycan                                                                  | Upregulated     |                                                  |                  |                        |
| ATOH8, DMRT2, |                                                                           |                 |                                                  |                  |                        |
| TBX15, ZNF367 |                                                               |                 |                                                  |                  |                        |
| Myoferlin    | Myoferlin                                                                 | Upregulated     | Associated with tumor progression               | Blomme et al., 2016 | Breast cancer           |
| ACSL4        | Fatty acetyl-Co A Synthase                                                | Upregulated     | Associated with development and progression of tumor | Marie et al., 2010 | Breast cancer           |
| FNDC5/Irisin, | Fibronectin type III domain , sterol regulatory element binding protein, Stearoyl Co-A desaturase | Upregulated     | Associated with inflammation and cancer progression | Gaggini et al., 2016 | Hepatocellular carcinoma |
| SNHG16       | SNORNA host gene                                                          | Upregulated     | Associated with tumorigenesis                   | Christensen et al., 2016 | Colorectal cancer       |

by Bansal et al. showed that in the United States and Europe, the incidence of hepatocellular carcinoma is increasing more rapidly in younger generations. The authors demonstrated that SCD1 plays a significant role in the biosynthesis of MUFAs. SCD1 acts as an essential regulator and is expressed at high levels in multiple human hepatocellular cancer cell lines. The authors also discovered that when these cell lines were treated with a set of chemotherapeutics, SCD1 gene expression increased. Moreover, a correlation was identified between increased enzyme expression and the degree of tumor differentiation.

SCDs also play a critical role in the biosynthesis of saturated fatty acids (SFAs) and MUFAs. A number of reactions occur in cancer cells to support the continuous synthesis of SFAs and MUFAs; these reactions involve enzymes such as adenosine triphosphate-citrate lyase,
acetyl-CoA carboxylase (ACC), FAS, and SCD.\textsuperscript{[53]} Any alterations in these enzymes disturb the balance of SFAs and MUFAs within the cell and drastically alters the cellular functions of SFAs and MUFAs. In particular, MUFAs play a vital role in the regulation of cell proliferation and programmed cell death. SCD1 shares a common molecular link with various pathological disorders that have been associated with cancer. According to the literature review, major events could be involved in the upregulation of SCD in various human cancers, for example, regulation of the rate of fatty acid biosynthesis, the generation of MUFAs for lipid macromolecule formation, and alterations in signaling networks that maintain the expression and activity of key enzymes of lipid metabolism. SCD1 activity may facilitate the high fatty acid biosynthetic rate by modulating ACC, the key regulatory enzyme in this pathway.

Lipid biosynthetic pathways, such as the fatty acid synthesis and desaturation pathways, are the most promising molecular targets for cancer therapy. The inhibition of SCD1, the enzyme that produces MUFAs, impairs cancer cell proliferation, survival and invasiveness and dramatically reduces tumor formation. CVT-11127, C75, cerulenin, and TOFA are novel small-molecule inhibitors of SCD activity that result in SCD1 depletion, leading to reduced lipid synthesis, impaired proliferation stemming from cell cycle arrest at the G\textsubscript{1}/S transition, and the triggering of programmed cell death. These inhibitors were found to be effective at blocking SCD activity in human cancer cell lines by decreasing the rate of cell proliferation in oncogene-transformed cancer cells. A decrease in the rate of proliferation of SCD1-deficient cells indicated that SCD1 is involved in a crucial metabolic step that is common to many cancer-cell types. Genetic and pharmacological inhibition of SCD1 triggers AMPK activation and impairs de novo fatty acid synthesis from glucose. By controlling SFA levels through conversion into MUFAs, SCD1 modulates the rate of fatty acid synthesis and consequently, of overall glycerolipid biosynthesis.
Moore et al.\textsuperscript{[44]} stated that a reduction in SCD expression contributes to the development of human prostate carcinoma. Several mechanisms are possibly responsible for the reduction in SCD. Regulators of tumor cell growth have been shown to modulate SCD expression, and alterations in SCD levels influence signaling pathways important for cell growth and metabolism. SCD deficiency enhances signaling through the insulin receptor (IR) pathway, as demonstrated by an increase in basal phosphorylation of IR, IR substrate (IRS)-1 and IRS-2; increased association of IRS-1 and IRS-2 with PI3K; and increased phosphorylation of Akt.\textsuperscript{[44]} The activation of the PI3K/Akt pathway has been shown to be important for regulating the proliferation, apoptosis, and growth of many cancers, including prostate carcinoma.

**Fatty acid synthase**

Fatty acid synthase (FASN) is another gene that was found to be upregulated in many studies. The FASN enzyme plays an essential role in lipid synthesis. Long-chain fatty acids are produced from acetyl-CoA and malonyl-CoA. Low expression levels and activity of FASN are tightly regulated by hormones, diet and growth factors. \textit{De novo} fatty acid synthesis occurs in proliferating cancer cells to provide lipids for membrane formation and energy production, as shown in Figure 3. FASN expression was been reported to be highly associated with oncogenic activity in several cancers, such as prostate, ovarian, breast, endometrial, thyroid, colorectal, bladder, lung, thyroid, oral, tongue, esophageal, hepatocellular, pancreatic, and gastric carcinoma. Poor prognosis and a lower survival rate have been found to be strongly associated with increased FASN expression in different cancer types. FASN plays a vital role in tumor development, progression, and survival, which has been confirmed in previous studies involving siRNA knockdown of FASN in tumors.\textsuperscript{[47,55]} FASN is a biosynthetic enzyme that is involved in neoplastic lipogenesis. While accumulating evidence for this literature review, we found that FASN overexpression was common in many human cancers, suggesting that it is a metabolic oncogene with an important role in tumor growth and survival and thus an attractive target for cancer therapy. The regulation of FASN expression in cancer is complex.\textsuperscript{[46]}

Microenvironmental stresses play a role in regulating FASN expression through growth factor receptors, such as ERBB-2 and epidermal growth factor receptor (EGFR), which interact and trigger the downstream PI3K/AKT and MAPK signaling pathways, leading to the upregulation of FASN expression. Aberrant activation of AKT and MAPK leads to FASN overexpression in hormone-sensitive organs such as the breast, ovary, and prostate through the activation of sex hormone receptors by estrogen, progesterone, and androgen.

**Fatty acid binding protein 4**

FABP4 has been increasingly thought to play an essential role in cancer progression. Regarding various metabolic functions, FABP4 is responsible for the conversion of various fatty acids to cellular compartments. FABP4, an adipokine, also plays an important role in numerous critical cellular processes, such as the regulation of gene expression and cell proliferation and differentiation. FABP4 has been suggested as a new prognostic indicator in bladder cancer and ovarian cancer, as well as in obese patients with breast cancer. Overexpression of FABP4 in glioblastoma acts as proangiogenic factor because FABP4 expression is regulated by VEGF. FABP4 promotes prostate cancer progression and provides an interaction point between fat cells or adipocytes in the bone marrow. Guaita-Esteruelas\textit{ et al.}\textsuperscript{[14]} stated that FABP4 protein could be regarded as a potential target for the treatment of different types of cancer, as it was discovered as a significant protein responsible for ovarian cancer cell migration.

**Most commonly involved pathway in lipid metabolism in cancer**

The most commonly involved in lipid metabolism in cancer was the PI3K/Akt signaling pathway. PI3K catalyzes the production of the lipid second messenger phosphatidylinositol-3,4,5-triphosphate (PIP3) at the cell membrane. Cell proliferation, survival, growth, and motility are among the various normal cellular processes controlled by the PI3K/Akt signaling pathway and are critical for tumorigenic growth.\textsuperscript{[47]} In oncogenesis, the PI3K/Akt pathway has been more widely investigated, and altered expression and abnormal mutation of this pathway have been associated with cancer. PI3K was first identified as an essential enzyme responsible for

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure3.png}
\caption{Regulation of fatty acid synthase in cancer: SREBP1-c: Sterol elementary binding protein, MAPK: Mitogen-activated protein kinase, PI3 kinase: Phosphoinositide 3-kinase, Akt: Protein kinase B}
\end{figure}
TOFA was found to be the most common inhibitor used to suppress tumor growth. Mason et al.\textsuperscript{[30]} identified TOFA as a potential SCD1 inhibitor by using a fatty acid strategy to describe various inhibitors of fatty acid synthesis. Guseva et al.\textsuperscript{[80]} stated that TOFA decreases fatty acid synthesis; inhibits the expression of androgen receptor (AR), neuropilin-1 and Mcl-1; and kills prostate cancer cells independent of p53 status. Li et al.\textsuperscript{[33]} reported that TOFA enhances caspase-3 activity and inhibits fatty acid synthesis by inducing the apoptosis of ovarian cancer cells.

**Current perspective**

In cancers such as lung, breast, and prostate cancer, lipid metabolism plays an essential role, but its role in oral cancer has not been adequately researched. Very few studies have described the role of lipid metabolism in oral cancer. Based on accumulated data, SCD1 has arisen as a crucial factor involved in cancer development and progression. SCD1 is considered a chief participant in the regulation of lipid synthesis, but its role in oral cancer has not been investigated. In the future, further investigations should be carried out on the regulation of signaling pathways, and genes involved in lipid metabolism in oral cancer with a larger sample size to provide rational targets.

**Conclusion**

In the present study, 38 genes involved in lipid metabolism in cancer were analyzed; among these genes, SCD1 was the most commonly reported. SCD1 is a major participant in the modulation of lipid synthesis. FASN is another gene that was found to be upregulated in many studies and is known for its significant role in lipogenesis. Akt kinase pathways are considered dynamic areas of study in the regulation of metabolism in cancer, although we have a very limited understanding of the integration of these two processes by Akt family members. SCD1 and FASN play substantial roles in the initiation and progression of cancer, these genes could possibly be attractive anti-cancer targets in the near future.

Most of the studies considered for this systematic review were conducted on cell lines and animal models, whether the same expression of proteins/genes will be obtained in human tissue requires more studies in the future on human biological samples. Increasing evidence in the literature suggests that oncoproteins have a direct effect on reprogramming cancer cell metabolism and making them addicted to certain metabolic pathways. Future investigations with a large sample size should focus on elucidating the mechanism by which signaling pathways regulate lipid metabolism. This would generate novel therapeutic strategies for the development of anti-cancer drugs.

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Conflicts of interest
There are no conflicts of interest.

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