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Targeting lipid metabolism for the treatment of Anaplastic Thyroid Carcinoma

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Abstract

Introduction—Anaplastic thyroid carcinoma (ATC) is the rarest subtype of thyroid cancer, however it disproportionately accounts for a large percentage of all thyroid cancer related deaths and is considered one of the most lethal solid tumors in humans, having a median survival of only a few months upon diagnosis. While a variety of treatment options are available including surgery, radiation and targeted therapies, response rates are low, due in part to the drug-resistant nature of this disease; therefore, new avenues for therapeutic intervention are surely needed. Recent investigation into the metabolic profile of ATC has revealed a tumor-specific dependency for increased *de novo* lipogenesis, offering new insight into the molecular mechanisms that govern disease initiation and progression.

Areas Covered—Herein we summarize known oncogenic signaling pathways and current therapeutic strategies for the treatment of ATC. We further discuss the unique expression pattern of lipid metabolism constituents in this disease. Additionally, the current literature correlating aberrant lipogenesis with carcinogenesis is reviewed, and the implications of targeting this pathway as an innovative approach for treating ATC and other malignancies is discussed. As stearoyl-CoA desaturase (SCD) is the most differentially expressed constituent of lipid metabolism in ATC, an additional focus on this enzyme as a novel therapeutic target is applied.

Expert Opinion—This section is used to summarize the current research efforts underway in defining the role of lipid metabolism specifically in thyroid carcinoma. Included is a brief summary of lipid metabolism factors for which inhibitors have been generated and are under current investigation as anti-cancer agents. Finally, research limitations regarding the use of these inhibitors against components of this pathway are discussed.

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Keywords

De novo lipogenesis; lipid metabolism; anaplastic thyroid carcinoma; stearoyl-CoA desaturase; fatty acid synthase; sterol regulatory-element binding protein; carcinogenesis; chemoresistance; fatty acids

1. Common genetic anomalies in ATC

Anaplastic thyroid carcinoma (ATC) is thought to arise from pre-existing well-differentiated thyroid carcinomas (WDTC) through the acquisition of additional genetic deviations. This has been deciphered through multiple genetically engineered mouse models that progress from follicular and papillary WDTC to undifferentiated ATC¹. Currently, numerous transformations in molecular mechanisms governing the development of thyroid malignancy and subsequent progression into poorly differentiated and ATC have been identified. These include activation of receptor tyrosine kinases, proliferative or pro-survival intracellular signaling pathways, abnormalities in cell cycle constituents, alterations in cytoskeletal components and regulators of mitosis, and overexpression of apoptotic inhibitors²⁻⁴. A summary of characterized mutations in ATC is listed in **Table 1**.

Activation of MAPK signaling has been demonstrated in well-differentiated as well as ATC tumors, facilitated by a number of mechanisms. Several RET-PTC translocations have been characterized in papillary thyroid carcinoma (PTC), and in particular *RET/PTC3* is often correlated with advanced disease and more aggressive phenotype⁶. Activating point mutations in RET are frequently observed in medullary thyroid carcinoma (MTC)⁷. Oncogenic RET signaling results in increased tyrosine kinase activity of this receptor and subsequent stimulation of MAPK and PI3K/AKT pathways⁷. ATC lesions arising from WDTC may also demonstrate RET hyperactivation²⁻⁵. Mutations in BRAF are also observed in both PTC and ATC, leading to activation of its downstream effector MEK.

The small GTPase RAS, also mutated in follicular thyroid carcinoma (FTC) and ATC, is known to govern a variety of pro-survival pathways including both MAPK and PI3K/AKT. Dysregulation of PI3K/AKT has also been demonstrated in all thyroid malignancies via genetic silencing or inactivating mutations in the tumor suppressor PTEN or activating point mutations in PI3KCA²⁻⁵. AKT activation conveys tumor cell survival and growth through a multitude of molecular mechanisms including mTOR signaling.

TP53 gene alterations are frequently observed in poorly differentiated thyroid carcinomas and ATC^{8,9}, likely leading to disruption of cell cycle checkpoints and DNA repair machinery, resulting in tumor cell tolerance of accumulating genetic instabilities. Loss of molecular mechanisms governing cell polarity such as mutations in CTNNB1 are frequently observed in ATC², and likely facilitate tumor cell dissemination and invasion.

Finally, vascular homeostasis is lost in ATC though tumor-associated overexpression of VEGF, PDGFR and other angiogenic factors^{2,5}. This neovascularization results in the formation of tortuous vessels, abnormal perivascular coverage, and irregular extracellular matrix deposition. Not only does this contribute to tumor cell growth, but also enhances

intravassation, metastasis, and drug resistance due to increased oncotic pressure resulting from leaky vasculature¹⁰.

2. Current targeted therapies and their efficacy in ATC

Several targeted therapies are currently under clinical investigation to evaluate their efficacy against ATC, and are largely based on the genetic profile of ATC tumors. These include tyrosine kinase blockade of RET, VEGFR1-2, PDGFRA, BRAF and EGFR using either small molecule or antibody mediated inhibition. Vascular disrupting agents as well as other novel compounds are also in clinical testing. A summary of agents investigated in a clinical setting are provided in **Table 2**.

Unfortunately ATC is largely chemo and radiation resistant, and develops drug-resistance rapidly despite the current availability of targeted therapeutics²⁴. Furthermore, while surgery often conveys a survival advantage in patients with ATC, it is not curative, and advanced local and distant metastasis often renders ATC prodigally unresectable^{2, 25, 26}. For patients who can tolerate aggressive treatment, tumor debulking followed by radiation and chemotherapy is the current recommended course of therapy. It is clear that even current targeted therapies only modestly prolong patient survival, and therefore new avenues of targeted therapeutics must be explored.

3. De novo lipid biosynthesis in ATC

Recently, a renewed emphasis on cancer-associated metabolic changes has shed light on dysregulated activation of *de novo* fatty acid and cholesterol biosynthesis. Normal adult mammalian tissues derive the majority of lipid molecules from the diet through the blood stream either in the form of free fatty acids or lipoproteins²⁷. *De novo* lipid biosynthesis is tightly regulated, predominantly occurring in the liver, intestines, adipose tissue, and lactating mammary tissues²⁷. It was established over 60 years ago that neoplastic tissues demonstrate a higher lipogenic need, suggestive of either increased uptake from the host or accelerated biosynthesis to support tumorigenesis²⁸. Upregulation of fatty acid transport proteins has been observed in cancer, allowing these cells to provision free fatty acids from the extracellular environment²⁹. More recent publications highlight specific overexpression of various constituents of lipid biosynthesis in a variety of tumors as well as tumor cell sensitivity to targeted inhibition of these components, thereby demonstrating a tumor-specific requirement for lipid metabolism^{27, 30-33}. Tumors that demonstrate a lipogenic phenotype are often correlated with disease aggressiveness, and frequently exhibit poorer patient outcomes^{30, 34}.

Gene array analysis of ATC tissue compared to normal thyroid tissue reveals increased expression of machinery that facilitates *de novo* fatty acid biosynthesis. These include acetyl-CoA carboxylase alpha (ACC), fatty acid synthase (FASN), and several fatty acid elongase and desaturase enzymes including both human isoforms of stearoyl-CoA desaturase (SCD1, SCD5)³⁵. In addition, a variety of proteins whose roles include fatty acid uptake, transport, and metabolism are upregulated including several fatty acid binding

proteins (FABP) and solute carrier family 27 (SLC27A) proteins³⁵. Taken together, this suggests an increased need for lipid bioavailability in this malignancy.

4. Lipid metabolism and the tumorigenic phenotype

Currently it is not well understood what specific elements of lipid biosynthesis support neoplastic transformation and tumor progression, however alterations in any number of lipid metabolism enzymes, transcription, factors, etc. involved in normal cellular processes can plausibly affect cell growth, signaling, and motility. Synthesis of saturated fatty acid molecules by FASN, and subsequent modification by a variety of elongase and desaturase enzymes, including SCD, produces a variety of saturated and unsaturated fatty acids that are substrates for membrane phosphoglyceride and triacylglyceride synthesis²⁷. Membrane phosphoglycerides are critical for membrane synthesis, influence membrane fluidity and permeability, regulate membrane protein docking, incorporation and turnover, are involved in the synthesis of prostaglandins and other inflammatory species, and are important in numerous signaling pathways that regulate cell survival, mobility, and growth^{27, 36}.

Triacylglycerides can be used for long-term energy storage, or can be transported to the mitochondria where they are subject to β -oxidation, producing NADH, FADH₂, and acetyl-CoA which can re-enter the TCA cycle²⁷. Activation of the mevalonate pathway in cancer cells leads to the production of cholesterol. As with fatty acids, cholesterol molecules can be incorporated into lipid bilayer structures where they influence membrane fluidity, receptor clustering, and endo/exocytosis²⁷. Cholesterol also serves as a building block for numerous steroid-based signaling molecules. In addition, the mevalonate pathway drives isoprenoid synthesis which is important for the prenylation of a wide variety of proteins. One notable example of this is the oncoprotein Ras, which is frequently activated in thyroid malignancies. Addition of lipid moieties subsequently modifies its ability to interact with and activate target proteins or substrates³⁶.

Several malignancies, such as glioblastoma and prostate cancer, demonstrate oncogenic activation of sterol regulatory element-binding proteins (SREBP)^{37, 38}, a transcription factor that is critical in regulating multiple facets of lipid metabolism through controlled expression of a large number of lipogenic factors involved in cholesterol and fatty acid metabolism, triacylglyceride synthesis, and plasma lipoprotein metabolism^{39, 40}. SREBP activity is typically governed by intracellular levels of cholesterol and fatty acids^{39, 40}. It has been recently reported that aberrant upstream signaling through receptor tyrosine kinases, AKT, and mTOR- pathways commonly altered in cancer, may promote SREBP processing and activation thereby driving *de novo* lipogenesis^{29, 37}. Guo et al. demonstrated glioblastoma cell sensitivity to an inhibitor of SREBP-1 processing, resulting in decreased proliferation. In addition, this group presented anti-tumor efficacy in a preclinical model of glioblastoma using a pharmacological inhibitor of FASN, a transcriptional target of SREBP-1⁴¹, strongly supporting the need for increased lipid metabolism in this cancer.

FASN over-expression and activity has been extensively studied in breast cancer, and is correlated with numerous functions that enhance tumorigenesis. These include membrane phospholipid and lipid raft synthesis, receptor tyrosine kinase activation, DNA replication,

fatty acid β -oxidation, and activation of survival signaling pathways such as Akt³⁰. Elegant work by Rysman et al, demonstrates that activation of *de novo* lipogenesis and resulting accumulation of saturated and mono-unsaturated lipid species (specifically the products of FASN and SCD enzymatic activity) modulate the biophysical properties of cancer cell lipid membranes by promoting their saturation, resulting in reduced sensitivity to lipid peroxidation as well as treatment with H₂O₂ and chemotherapy⁴². These findings suggest that lipogenic tumors may demonstrate increased resistance to chemotherapy and are also protected against oxidative stress. Paton et al. 2010 similarly correlated SCD desaturase activity with membrane homeostasis in breast cancer cells, where targeted inhibition of SCD led to increased free cholesterol levels, decreased cholesterol esterification, and affected cholesterol efflux. Increased lipid raft formation due to membrane incorporation of free cholesterol was observed, and was predicted to affect membrane fluidity⁴³.

Several groups have also correlated oleic acid production with increased tumor cell migration and invasiveness^{44, 45}. Work done by Vazquez-Martin et al. found that *de novo* lipogenesis is activated in induced pluripotent stem cells (iPS), and that pharmacological inhibition of FASN or ACC hinders reprogramming efficiency⁴⁶. This suggests a potential role for lipid biosynthesis in tumor stem cell generation and proliferation. A role for SCD activity in autophagosome formation has also been reported⁴⁷. As autophagy is commonly associated with cancer cell survival and drug resistance⁴⁸, this further implicates a role for lipogenesis in tumor viability and progression. A brief summary of lipid metabolism is provided in **Figure 1**, including upstream signaling implicated in tumor-associated lipogenesis, and biological function resultant of specific components of this pathway.

5. Stearoyl-CoA desaturase as a therapeutic target in ATC

Of the lipogenic enzymes upregulated in ATC, SCD is the most significantly differentially expressed compared to normal thyroid tissues³⁵. Additionally, protein expression of this enzyme is increased in WDTCs including PTC and FTC. SCD is a fatty acyl desaturase enzyme whose functional role is to catalyze the conversion of saturated fatty acids produced by FASN activity into mono-unsaturated fatty acids through insertion of a *cis*-double bond at the 9 position of the carbon chain⁴⁹. To date, five isoforms of this enzyme have been characterized, of which two are expressed in humans- SCD1 and SCD5⁵⁰. SCD1-4 were identified and characterized in the mouse genome⁵⁰. Each of these isoforms demonstrates differential tissue distribution and expression patterns, yet maintains conserved enzymatic function⁵⁰. In ATC, therapeutic and genetic targeted inhibition of SCD enzymatic activity facilitated a robust decrease in cell proliferation and induced cell death where normal thyroid cells remained unaffected³⁵. Interestingly, tumor cells derived from well-differentiated lesions demonstrate resistance against SCD inhibition, and suggest a specific vulnerability in the more aggressive thyroid malignancy to this treatment.

Loss of SCD enzymatic activity in ATC correlates with an induction of the endoplasmic reticulum (ER) stress response, resulting in the activation of a variety of chaperone, degradation, and pro-apoptotic proteins. This is consistent with other research studies focusing on SCD in cancer as well as metabolic disorders. In cancer, SCD inhibition demonstrates activation of ER stress and inflammation in a variety of tumor models

including colorectal adenocarcinoma⁵¹, non-small cell lung carcinoma⁵², and renal cell carcinoma³³, resulting in tumor cell death. SCD activity has also been shown to play a key role in modulating diabetes by reducing ER stress, inflammation, and insulin resistance by converting lipotoxic substrates such as stearate and palmitate into monounsaturated fatty acid species in primary patient-derived myotube models⁵³. Green et al. reported that expression of SCD1 and the fatty acid elongase ELOVL6 could protect pancreatic β -cells from ER stress and apoptosis induced by exposure to elevated free fatty acids- a potent risk factor for type 2 diabetes and insulin resistance in a rodent model of diabetes⁵⁴. Given the numerous reports linking the loss SCD enzymatic activity with heightened ER stress and inflammation, it is plausible that these intracellular responses are culpable for increased cancer cell death as a result of tumor-specific dependency on this pathway.

Considering the reported biological diversity involving SCD activity and other constituents of *de novo* lipogenesis in tumor cell chemoresistance, protection from cellular stress, proliferation and migration, and energy storage and metabolism, it stands to reason that targeted inhibition of this pathway may be used successfully in combination with a variety of existing anti-cancer regimens for the treatment of ATC. When combined with the proteasome inhibitor carfilzomib, the SCD inhibitor MF-438 showed reduced tumor growth in a preclinical model of ATC³⁵. In addition, several recent examples of successful combinatorial therapy involving agents targeting lipid metabolism in models of cancer have been established. FASN inhibitors demonstrate good anti-tumor efficacy in cell models of prostate cancer when used in combination with thiazolidinediones (TZDs), a family of PPAR γ activators⁵⁵. In a preclinical model of colorectal carcinoma, the FASN inhibitor cerulenin when used in combination with oxaliplatin chemotherapy significantly decreased tumor growth when compared to monotherapy⁵⁶. The SCD inhibitor A939572 when tested in a preclinical model of clear cell renal cell carcinoma combined with temsirolimus, an mTOR inhibitor, demonstrated anti-tumor synergy³³.

6. Expert Opinion

The disequilibrium in the expression of lipid metabolism constituents in ATC is strongly suggestive of increased lipogenesis in these tumors. Our work and that of others support that various components of this pathway may serve as attractive therapeutic targets for the treatment of a variety of cancers. Currently, little to no investigation into the role of lipogenesis as a pro-tumorigenic mechanism specifically in ATC, or other subtypes of thyroid cancer has been done. Wojakowska et al. recently published on the application of metabolomics as a useful tool in the investigation of thyroid malignancy, summarizing notable discrepancies in the expression of various lipid constituents between normal and malignant thyroid tissue⁵⁷. Lovastatin, an inhibitor of HMG-CoA reductase (HMGCR), has been shown to demonstrate anti-tumor efficacy in ATC through targeted inhibition of mevalonate synthesis and blockade of geranylgeranylation and subsequent Rho GTPase activation⁵⁸. Recently published work by our group represents one of the first comprehensive analyses of lipid metabolism profiling in ATC³⁵. As such, there is a need for additional investigation of lipid metabolism in the context of ATC and thyroid carcinoma in order to improve our understanding of its contribution toward the initiation and progression of this disease, and define additional appropriate therapeutic targets.

Given the tumor-specific over-expression of particular lipid metabolism genes in ATC, and the strict regulation of this pathway in normal tissue, it stands to reason that targeted inhibitors may be predicted to produce discriminative therapeutic responses in diseased tissue. This presents an entirely new venue in which several candidate therapeutic targets may be explored and identified. Currently inhibitors against a variety of enzymes involved in *de novo* lipogenesis have been produced and are under investigation for anti-tumorigenic efficacy including ACC, ATP citrate lyase (ACL), carnitine palmitoyltransferase 1 (CPT-1), FASN, monoacylglycerol lipase (MAGL), HMGCR, SCD, and SREBP1^{36, 59-61}.

Acquired resistance to monotherapeutic applications remains a challenge given the heterogeneous nature of ATC and other aggressive malignancies. While limited efficacy was observed in a preclinical model of ATC treated solely with an SCD inhibitor, a significant combinatorial effect with a proteasome inhibitor was observed³⁵. Thus, while various inhibitors of lipid metabolism should be individually investigated for anti-tumor efficacy, combinatorial applications with complementary regimens including radiation, chemotherapy, and other targeted agents should also be explored.

One of the most notable impediments in the progression of lipid metabolism research in cancer is the use of rodents as preclinical models. While generally observed as convenient tools to evaluate therapeutic efficacy, the vast discrepancies in genetic variation, tissue distribution, expression, and regulatory mechanisms governing lipid metabolism limit their translational relevance in humans⁶². For example, murine models express four isoforms of SCD, only one being homologous to human SCD⁵⁰. Therefore, adverse events observed in rodent models in response to SCD inhibitors may not necessarily be predictive of toxicity profiles in humans. Alternative preclinical models that more accurately reflect lipid metabolism observed in humans may be necessary in order to enhance the prognostic value of targeting this pathway not only in cancer, but other diseases as well.

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Reference annotations

* Of interest

** Of considerable interest

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Article Highlights

- This article provides a brief review of the known oncogenic factors in ATC.
- This article summarizes the current targeted therapies for ATC and results of clinical evaluation.
- A brief review of cancer-associated lipid metabolism is provided, and pro-tumorigenic mechanisms of aberrant lipogenesis are highlighted.
- Constituents of lipid metabolism currently under investigation as novel therapeutic targets are discussed.
- Abnormal expression of *de novo* lipogenesis in ATC is examined.
- Targeting SCD as well as other metabolic enzymes as a treatment for this variant of thyroid cancer, either alone or in combination with other therapies, is discussed

Figure 1. Summary of lipid metabolism

A brief summary of lipid metabolism signaling including fatty acid synthesis and components of the mevalonate pathway thought to be important in the pathogenesis of cancer. Activation of Receptor Tyrosine Kinases (RTKs) such as EGFR or HER2/neu through ligand binding, receptor overexpression, or activating mutations are thought to promote a variety of intracellular signaling pathways such as PI3K/AKT. AKT activation in turn stimulates mTOR, resulting in SREBP processing and activation through blockade of LIPIN1. SREBP is a potent transcription factor that recognizes and binds to sterol regulatory elements (SRE) within the genome, inducing transcription of these target genes that include numerous factors involved in lipid metabolism and fatty acid uptake. Tumor cells also may increase lipid bioavailability through increased Free Fatty Acid (FFA) uptake via upregulation of fatty acid transport receptors and chaperones such as CD36, Solute Carrier Family 27/Fatty Acid Transporter (SLC27A/FATP), and Fatty Acid Binding Proteins (FABP). In addition, metabolic reprogramming that facilitates glycolysis, a common phenomenon in tumorigenesis known as the Warburg effect, can activate *de novo* lipogenesis. Acetyl-CoA derived from citrate can be further processed into a variety of lipid species via the activity of various enzymes. Cholesterol and free fatty acids are important for a variety of cellular functions including membrane synthesis, inflammation, fatty acid β -oxidation, energy storage, cholesterol synthesis, protection from cellular stress, post-translational modification of proteins through prenylation, and cellular communication. Lipid metabolism enzymes that are current therapeutic targets of interest for the treatment of

cancer are bold-faced. Enzymes are italicized. Abbreviations: ACL- ATP Citrate Lyase ; ACC- Acetyl-CoA Carboxylase Alpha; EGF- Epidermal Growth Factor; FGF- Fibroblast Growth Factor; FASN- Fatty Acid Synthase; FFA- Free Fatty Acid; GLUT- Glucose Transporter; HMGCR- Hydroxymethylglutaryl-CoA Reductase; IGF- Insulin-like Growth Factor; LDLR- Low Density Lipoprotein Receptor; PDH-Pyruvate Dehydrogenase; RTK- Receptor Tyrosine Kinase; SCD- Stearoyl-CoA Desaturase; TGF- Transforming Growth Factor. A small 'p' indicates a phosphorylation event.

Table 1

Common mutations in ATC

Gene	Relative Prevalence (%)	Reference
<i>BRAF</i> ^{V600E}	23-26	2, 4, 5
<i>RET/PTC</i>	0-4	4, 5
<i>RAS</i>	20-22	2, 4
<i>PTEN</i>	4-16	2, 4, 5
<i>PI3KCA</i>	11-24	2, 4, 5
<i>TP53</i>	48-55	2, 4, 5
<i>CTNNB1</i>	25-60	2, 5
<i>Axin</i>	82	2
<i>APC</i>	9	2
<i>TERT</i>	33-50	5

Table 2

Summary of Targeted Therapy in ATC

Targeted therapy	Trade Name	Molecular Target	Clinical Evaluation	No. ATC Patients	PR	SD	PD	Median Survival (months)	Reference
Sorafenib	Nexavar®	BRAF, VEGFR, c-KIT, RET, PDGFRA	Phase II	2/30			2		11
			Phase II	4/58		1	3		12
			Phase II	16				3.5	13
			Phase II	20	2	5		3.9	14
Dabrafenib	Tafinlar®	BRAF	Phase I	1/14			1	11.3	15
Pazopanib	Votrient®	VEGFR, PDGFR, RET, c-KIT	Phase II	15				3.6	16
Imatinib	Gleevec®	ABL, c-KIT, PDGFR	Phase II	11				6	17
Axitinib	Inlyta®	VEGFR1-3, PDGFR, c-KIT	Phase II	2/60	1				18
Fosbretabulin	Zybrestat®	Vascular disrupting agent	Phase II	26	0	7	15	4.7	19
Fosbretabulin in combination with Paclitaxel/ Carboplatin	Zybrestat®	Vascular disrupting agent, microtubule stabilizer, DNA crosslinker	Phase I	80				5.2	20
Bardoxolone methyl		NRF2 agonist, NFKB	Phase I	4/47	1				21
Gefitinib	Iressa®	EGFR	Phase II	5/27		1			22
Efautazone in combination with Paclitaxel		PPAR γ agonist, microtubule stabilizer	Phase I	15	1	7	4	3.2-4.4	23

* PR-partial response; SD- stable disease; PD-progressive disease