LPCAT1 and Cancer Control

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LPCAT1 is an enzyme which facilitates the production of certain cell envelope lipid like particles. It has been analyzed as a cancer enhancer and it control a cancer control. We examine some of these issues.

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1 INTRODUCTION

As is well known malignant growths have a variety of ways of proliferating in their host. The process requires various sources of energy to accomplish this task. A recent paper discusses another possible mechanism.

As the recent article in Eureka notes[1]:

The finding, published in the July 11, 2019 issue of Cell Metabolism, suggests a potential target for new drugs.

"Cancers are characterized not only by major changes in their genomes, but also by profound shifts in how they take up and utilize nutrients to propel rapid tumor growth," said senior author Paul S. Mischel, MD, professor in the UC San Diego School of Medicine Department of Pathology and Ludwig member. "How do these diverse aspects fit together and can they be taken advantage of, for the benefit of patients?"

In the new study, conducted in collaboration with Benjamin Cravatt, PhD, professor at Scripps Research, and led by first author Junfeng Bi, PhD, in Mischel's lab, researchers identified an enzyme called LPCAT1, whose levels increase in cancer and which plays a key role in tumor growth by changing the phospholipid composition of the cancer cells' plasma membrane, allowing amplified and mutated growth factor signals to spur tumor growth.

LPCAT1 is an enzyme involved in a variety of lipid cycles. As such it finds itself at the heart of energy processing and transfer in cells. The Eureka article continues:

Without LPCAT1, tumors cannot survive. *When researchers genetically depleted LPCAT1 in multiple types of cancer in mice, including highly lethal glioblastomas (brain) and an aggressive lung cancer, malignancies shrank dramatically and survival times improved.*

The results, wrote the authors, demonstrate that LPCAT1 is an important enzyme that becomes dysregulated in cancer, linking common genetic alterations in tumors with changes in their metabolism to drive aggressive tumor growth."

It is not clear that devoid of LPCAT1 the cell will cease proliferation. Cells, especially malignant cells have a variety of mechanisms to avoid assaults on their spread. We also know that cancer cells have multiple alternative metabolic pathways[2]. They continue:

"Advances in DNA sequencing technologies have reshaped our understanding of the molecular basis of cancer, suggesting a new and more effective way of treating cancer patients," said Mischel. "However, to date, precision oncology has yet to benefit many patients, motivating a

[1] https://www.eurekalert.org/pub_releases/2019-07/uoc--usd071119.php

[2] https://www.researchgate.net/publication/322437754_Glucose_Warburg_Cancer_and_Pathways

deeper search into understanding how genetic alterations in tumors change the way cancer cells behave, and potentially unlocking new ways to more effectively treat patients.

"These results also suggest that LPCAT1 may be a very compelling new drug target in a wide variety of cancer types."

Indeed, if LPCAT1 is a viable target for a therapeutic then it cant be used as such. We will investigate this target in this brief note.

Now the authors in the above-mentioned paper by Bi et al note[3]:

Advances in DNA sequencing technologies have reshaped our understanding of the molecular basis of cancer, providing a precise genomic view of tumors. Complementary biochemical and biophysical perspectives of cancer point toward profound shifts in nutrient uptake and utilization that propel tumor growth and major changes in the structure of the plasma membrane of tumor cells. The molecular mechanisms that bridge these fundamental aspects of tumor biology remain poorly understood.

Here, we show that the lysophosphatidylcholine acyltransferase LPCAT1 functionally links specific genetic alterations in cancer with aberrant metabolism and plasma membrane remodeling to drive tumor growth.

Growth factor receptor-driven cancers are found to depend on LPCAT1 to shape plasma membrane composition through enhanced saturated phosphatidylcholine content that is, in turn, required for the transduction of oncogenic signals. These results point to a genotype-informed strategy that prioritizes lipid remodeling pathways as therapeutic targets for diverse cancers.

Clearly this seems to be a complex multistep process. We examine LPCAT and the various metabolic cycles it is involved in in this note.

[3] https://www.cell.com/cell-metabolism/fulltext/S1550-4131(19)30317-1

2 LPCAT1

We present some of the basic facts regarding LPCAT1 and its functioning in a cell.

2.1 FUNDAMENTALS

Let us begin with a brief definition and description of the gene expressed LPCAT1. From NCBI[4]:

This gene encodes a member of the 1-acyl-sn-glycerol-3-phosphate acyltransferase family of proteins. The encoded enzyme plays a role in phospholipid metabolism, specifically in the conversion of lysophosphatidylcholine to phosphatidylcholine in the presence of acyl-CoA.

This process is important in the synthesis of lung surfactant and platelet-activating factor (PAF). Elevated expression of this gene may contribute to the progression of oral squamous cell, prostate, breast, and other human cancers.

LPCAT1 is thus a critical element in the lipid process in a cell and given the cell walls being fundamentally lipid in nature the activation can result in the changing of the receptors and thus the activation of various genes. Some of these changes in receptors and pathway activation result subsequently in malignant transformations. This the lipid metabolism and its effects and transitions are of significant interest.

As Matsumoto et al note:

Lysophosphatidylcholine (LPC) is a bioactive proinflammatory lipid generated by pathological activities. LPC is also a major phospholipid component of oxidized low-density lipoprotein (Ox-LDL) and is implicated as a critical factor in the atherogenic activity of Ox-LDL. LPC is believed to play an important role in atherosclerosis and inflammatory diseases by altering various functions in a number of cell-types, including endothelial cells, smooth muscle cells, monocytes, macrophages, and T-cells. LPC activates several second messengers -- including protein kinase C, extracellular-signal-regulated kinases, protein tyrosine kinases, and Ca(2+) -- implicating the engagement of transduction mechanisms in its observed actions. Moreover, recent evidence suggests that in several cell-types, cloned orphan G-protein-coupled receptors may serve as the specific receptors via which LPC modulates second messenger pathways (although LPC may not be a direct ligand of such receptors).

In addition, current evidence suggests that LPC impairs the endothelium-dependent relaxations mediated by endothelium-derived relaxing factors and directly modulates contractile responses in vascular smooth muscle. However, despite all this, and although elevated levels of LPC have been linked to the cardiovascular complications associated with atherosclerosis, ischemia, and diabetes, the precise pathophysiological roles played by LPC in several states remain to be established. In this review, we focus in some detail on the entirety of the signal-transduction

[4] https://www.ncbi.nlm.nih.gov/gene/79888

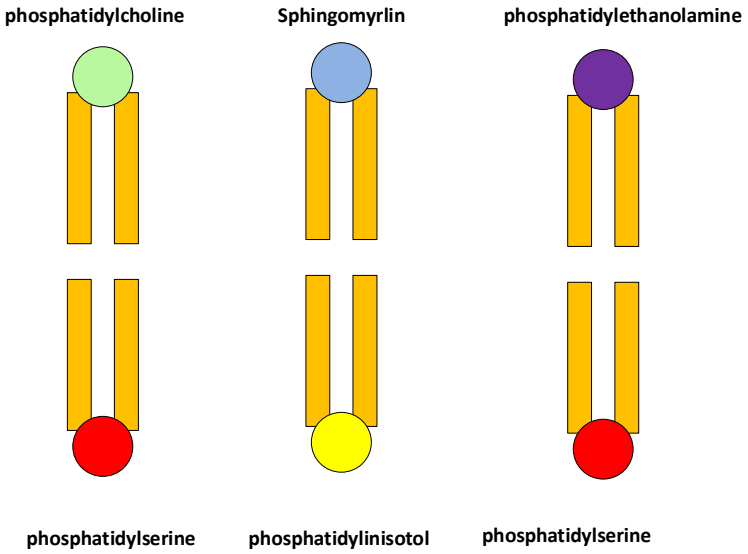
system for LPC, its pathophysiological implications, and the vascular abnormalities associated with it.

In comparison Li and Vance discuss phosphatidylcholine:

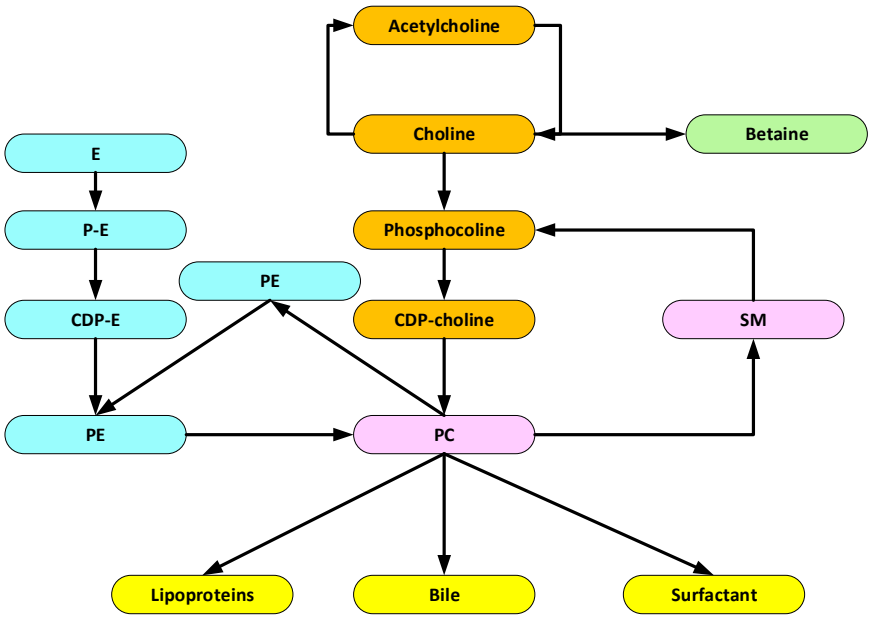
Phosphatidylcholine (PC) is an essential phospholipid in mammalian cells and tissues and is made in all nucleated cells via the choline pathway. Choline was first identified in ox bile by Strecker in 1862. The Greek word for bile is chole. After a long interlude, in 1932, Best and Huntsman discovered the choline deficiency that results in fatty liver in rodents when insufficient choline is provided in the diet. In animals, choline can be acquired from the diet and via de novo biosynthesis: choline is produced through the methylation of phosphatidylethanolamine (PE) to PC catalyzed by phosphatidylethanolamine N-methyltransferase (PEMT).

Choline can then be generated from PC via the action of phospholipases. The PEMT/phospholipase reactions constitute the only known endogenous pathway for choline biosynthesis in animals, whereas in plants and some microbes, choline can be made from the methylation of phosphoethanolamine (5–7). Thus, choline is made from the methylation of the ethanolamine moiety of phosphoethanolamine or PE. Both exogenous and endogenous choline is converted into PC, which accounts for 95% of the total choline pool in most animal tissues. The remaining 5% includes choline, phosphocholine, glycerophosphocholine, CDP-choline, and acetylcholine. In animals, PEMT is quantitatively significant only in the liver, and it accounts for 30% of hepatic PC biosynthesis in rodents. The other 70% of hepatic PC is made via the choline pathway.

The figure below shows the collection of lipid bilayer elements appearing in cells. The PC elements is depicted along with other similar elements.

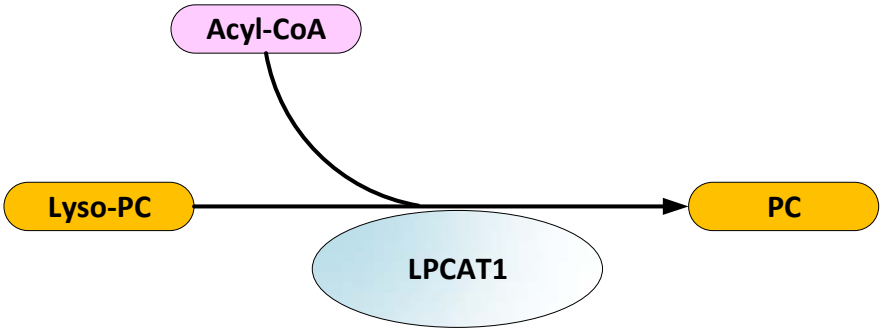


Li and Vance demonstrate this PC action in cells in the following figure[5]:



Note the central function of PC and its impact of major functions of a cell. The use of choline is a central part of this effort. But as previously demonstrated it is but one of several elements in the cell wall. Kisko presents the sectioned pathway as shown below (Note: Lyso-PhosphatidylCholine (PC) and Lyso-PhosphatidylCholine AcylTransferase 1 (LPCAT1))

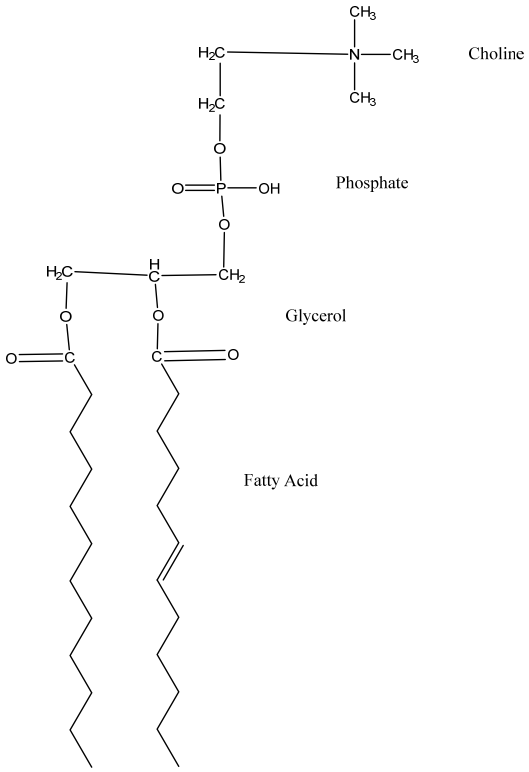
[5] Pathways involved in choline and phosphatidylcholine (PC) homeostasis. E, ethanolamine; P-E, phosphoethanolamine; CDP-E, CDP-ethanolamine; PE, phosphatidylethanolamine; SM, sphingomyelin. Enzyme names are indicated by numbers. 1, choline acetyltransferase; 2, choline kinase; 3, CTP:phosphocholine cytidylyltransferase; 4, CDP-choline:1,2-diacylglycerol cholinephosphotransferase; 5, sphingomyelin synthase; 6, phosphatidylserine synthase 1; 7, phosphatidylserine decarboxylase; 8, phosphatidylethanolamine N-methyltransferase; 9, ethanolamine kinase; 10, CTP: phosphoethanolamine cytidylyltransferase; 11, CDP-ethanolamine: 1,2 diacylglycerol ethanolaminephosphotransferase; 12, various phospholipase and lysophospholipase activities; 13, sphingomyelinase; 14, choline oxidase; 15, betaine aldehyde dehydrogenase.



See Kisko et al 2018

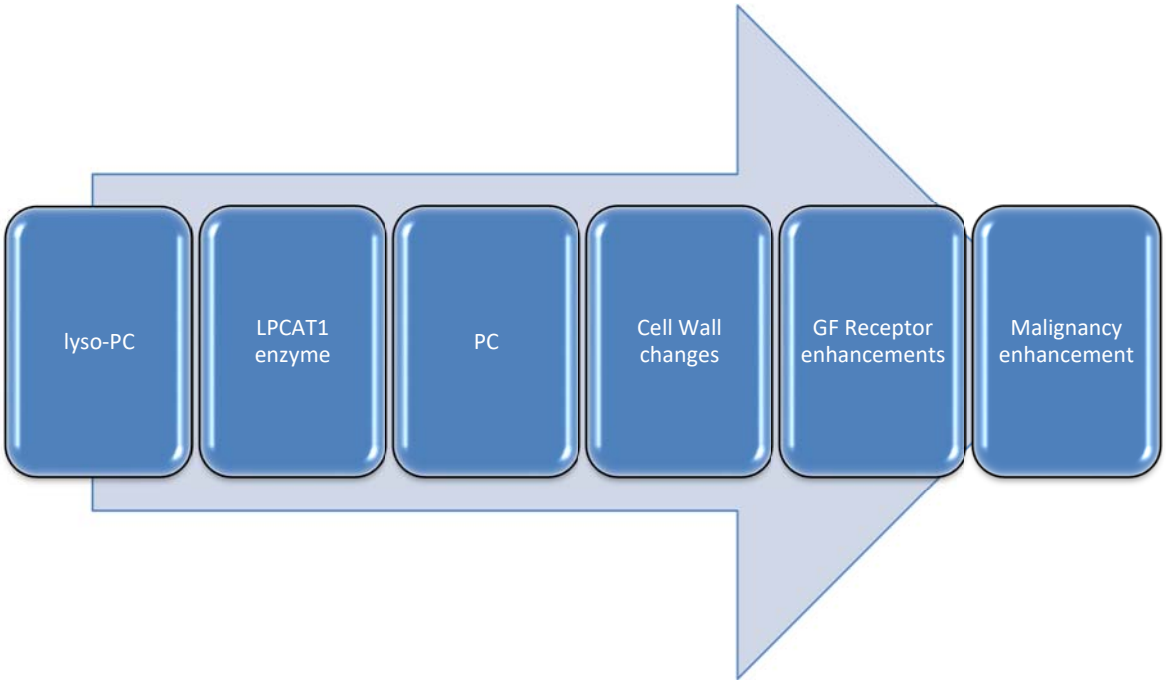
Loss of function mutations of *LPCAT1* affects the lysoPC/PC ratio in -Zn conditions. Schematic representation of the biochemical function of LPCAT1, which catalyses the formation of phosphatidylcholine (PC) from lyso-PC and long-chain acyl-CoA.

The PC molecule is shown below. Note the hydrophobic is the dual tail lipid and the hydrophilic is the top end with the choline. This is one of the collection of molecules which make up the cell wall. We show the PC molecule below[6]:



[6] See p 217, Litwack, Human Biochemistry, Academic, 2019.

Thus, LPCAT1 facilitates the production of the PC as shown above, then PC produces the dual lipids in cell walls, the lipids reconfigure the cell receptors and intensifying various receptor and growth factor effects and this accelerates the malignant state of the cell[7]. The idea then is if one blocks LPCAT1 does one then block the sequellae states and mitigate against malignancies? We demonstrate this conjecture below.



To understand the complete workings of lipids it is useful to summarize. This is done by Moessinger et al who note the complex interactions and lipid elements:

Lipids are important components of cells, with a function in cellular structure, regulation, signaling and as energy source, in particular neutral lipids. The cellular location of storage of neutral lipid is the lipid droplet (LD). LDs consist of a core of neutral lipids that is surrounded by a monolayer of phospholipids, mainly phosphatidylcholine.

Different proteins are associated with the LDs, including several enzymes of lipid metabolism. Many metabolic disorders like diabetes and cardiovascular diseases are associated with defects in lipid metabolism and derive from additive defects in different pathways, often described as metabolic syndrome that can gradually progress into more severe diseases. The first step is usually the excess storage of lipids within different body tissues resulting in the development of obesity.

Therefore, it is crucial to understand how the storage of lipids is regulated under normal conditions. Lipids are in a constant flux and are continuously converted into each other. Within

[7] https://www.researchgate.net/publication/329702571_Growth_Factors_Pathways_and_Cancers

cells they can move within membranes and between different cellular compartments. Furthermore, lipids are exchanged between different tissues.

Extracellularly, the bulk of lipids is transported in lipoproteins. These lipoproteins are soluble complexes of proteins (apolipoproteins) and lipids that are transported in the circulation of vertebrates and insects and that are synthesized in the liver and intestine. They are classified into chylomicrons (CM), very low density (VLDL), low density (LDL) and high density (HDL) lipoproteins based on their apolipoprotein component and their density, which is determined by the lipid composition.

The major neutral lipid, triacylglycerol (TAG), is secreted from the liver and intestine in apolipoproteinB (apoB) containing lipoproteins (CM and VLDL). In contrast to other apolipoproteins, apoB is not exchangeable between lipoproteins and resides in the plasma in a lipid-associated form only.

While VLDL and CM contain apoE, apoC and apoB, LDL harbors exclusively apoB. In the absence of loaded lipids apoB cannot be secreted and is rapidly degraded. The TAG secreted as CM and VLDL mainly derives from TAG stored in cytosolic LDs…In the Lands cycle phospholipase A2 (PLA2) removes fatty acids at the sn-2 position of PC, which results in the formation of lysophosphatidylcholine (LPC). This can be used in a reverse reaction, the addition of a fatty acid at the sn-2 position, to yield PC.

This re-acylation is catalyzed by lysophosphatidylcholine acyltransferases (LPCATs).

Recently, four LPCATs were cloned and characterized. They are all reported to localize to the ER compartment.

Due to their structure they divide into two subgroups with LPCAT1 and LPCAT2 in one and LPCAT3 and LPCAT4 in the other group.

LPCAT1 is reported to function in lung surfactant production, while LPCAT2 seems to be important in inflammatory reactions…

Essentially, our data now show that reduction of LPCAT1/2 results in unchanged balance between PC and TAG synthesis, along with a remodeling of LD morphology towards larger LDs, while reduction of the de novo pathway enzyme CT alpha changes the balance between PC and TAG synthesis towards the latter, accompanied by larger LDs and higher TAG content. Reduction of ER-localized LPCAT3/4 apparently does not influence neutral lipid storage. Also, knockdown of LPCAT1 decreases lipoprotein secretion by hepatoma cells.

As Zhou notes, as do many other authors, that malignancies often present with high LPCAT1 expression. This is explained in the following:

Lipid profiles provide useful information to determining the metabolic pathways of altered lipids in prostate cancer. In our previous studies, we found that the concentrations of all 14 detected lysophosphatidylcholine species are higher in both plasma and prostatic samples from patients with prostate cancer, as compared with samples from controls.

Further, we found that expression level of secretory phospholipase A2 (sPLA2) is increased in cancerous prostate as compared with benign prostate, which may contribute to the accumulation of lysophospholipid species in cancer tissues and in plasma (data not published).

Meanwhile, we also found that the expression level of lysophospholipid acyltransferase 1 (LPCAT1) is significantly higher in cancerous prostate as compared with benign prostate. Elevated expression of LPCAT1 also correlated with prostate cancer pathologic grade and clinical chemical recurrence in prostate cancer.

Taken together, cycle: tumor cells upregulate the expressions of both sPLA2 (which generate adequate lysophospholipid species, substrates for LPCAT1) and LPCAT1, in order to secure de novo synthesis of various phospholipid species for building cellular membranes of newly proliferated cancer cells.

By combining data of lipid profiles in individual species, cluster, group and class of lipids with lipid MAPS, more lipid metabolic pathways critical to prostate cancer could be identified.

Thus, LPCAT1 is a central figure as an enzyme. It produces PC and the excess production of PC facilitates the malignant status. PC apparently be suppressed by the suppression of LPCAT1 as noted earlier.

2.2 PATHWAYS

We demonstrated briefly the place of LPCAT1 in the production of the lipids in cell walls. Wei et al have noted:

Big data analysis can help us acquire more information about the mechanisms of the development and progression of tumors.

By searching tumor-related online databases and examining the gene expression in primary loci and adjacent tissues in healthy subjects and lung-cancer patients, we found that LPCAT1 was highly expressed in pulmonary tissues and its over-expression was correlated with the poor prognosis of NSCLC. LPCAT1 is a cytosolic enzyme that catalyzes the conversion of lysophosphatidylcholine (LPC) into phosphatidylcholine (PC) in remodeling the pathway of PC biosynthesis.

The high expression levels of LPCAT1 was not just with NSCLC but clearly across a wide spectrum of malignancies. They continue:

To date, LPCAT1 overexpression has been reported in clear cell renal cell carcinoma, oral squamous cell carcinoma, gastric cancer and breast cancer. LPCAT1 has been found to be a contributor to the progression, metastasis, and recurrence of cancer. However, reports on the role and the underlying mechanism of LPCAT1 in NSCLC have been scanty.

LPCAT1 was essential for the proliferation, migration and invasion of NSCLC in vitro. *Given that substantially higher LPCAT1 expression in LUAD tissues than in normal lung tissues according to TCGA LUAD and GEO datasets, we first looked into whether the elevated expression of LPCAT1 is associated with the development of NSCLC. Analysis of the TCGA datasets revealed that the copy number of LPCAT1 was directly proportional to its mRNA expression.*

In this presentation there is still an issue regarding just what LPCAT1 accomplishes to make is a accelerator of malignancies. The paper in question makes the argument for lipid layer production, yet even there the full nexus is left open for discussion. They continue:

Moreover, the expression of LPCAT1 in LUAD was significantly higher than in normal lung tissues and in lung squamous cell carcinoma. Additionally, we searched the THPA database to further examine the expressions of LPCAT1 in patients with various cancers. We found that LPCAT1 expression was relatively higher in patients with lung cancers than in those with other 16 tumors.

Moreover, search of the THPA dataset showed the positive rate of LPCAT1 was up to 80% in lung cancer tissues. *Together, these findings suggested LPCAT1 level increased in NSCLC tissues. Next, we performed PCR and Western blotting to assess LPCAT1 expression in NSCLC cell lines. As expected, both LPCAT1 mRNA expression and protein expression were found to be highly expressed in NSCLC cell lines.*

Understanding the overall effects and their causes has been a focus by many for a while. For example, Kisko et al note:

All living organisms require a variety of essential elements for their basic biological functions. While the homeostasis of nutrients is highly intertwined, the molecular and genetic mechanisms of these dependencies remain poorly understood.

Here, we report a ***discovery of a molecular pathway that controls phosphate (Pi) accumulation in plants under Zn deficiency. Using genome-wide association studies, we first identified allelic variation of the Lyso- PhosphatidylCholine (PC) AcylTransferase 1 (LPCAT1) gene as the key determinant of shoot Pi accumulation under Zn deficiency.***

We then show that regulatory variation at the LPCAT1 locus contributes significantly to this natural variation and we further demonstrate that the regulation of LPCAT1 expression involves bZIP23 TF, for which we identified a new binding site sequence. Finally, we show that in Zn deficient conditions loss of function of LPCAT1 increases the phospholipid Lyso-PhosphatidylCholine/PhosphatidylCholine ratio, the expression of the Pi transporter PHT1;1, and that this leads to shoot Pi accumulation.

They continue:

1. *LPCAT1 is involved in regulating shoot Pi concentration in Zn deficiency…*
2. *LPCAT1 acts downstream of bZIP23 transcription factor…*

3. *Allelic variation of LPCAT1 determines natural variation of Pi content under zinc deficiency…*
4. *LPCAT1 mutation impacts phospholipid concentrations in -Zn*

2.3 KENNEDY PATHWAY

One of the controlling pathways is the Kennedy Pathway. We discuss it briefly since understanding it may yield additional insight to control by therapeutics.

As Gibellini and Smith note:

The glycerophospholipids phosphatidylcholine (PC) and phosphatidylethanolamine (PE) account for greater than 50% of the total phospholipid species in eukaryotic membranes and thus play major roles in the structure and function of those membranes.

In most eukaryotic cells, PC and PE are synthesized by an aminoalcoholphosphotransferase reaction, which uses sn-1,2-diradylglycerol and either CDP-choline or CDP-ethanolamine, respectively.

This is the last step in a biosynthetic pathway known as the Kennedy pathway, so named after Eugene Kennedy who elucidated it over 50 years ago.

This review will cover various aspects of the Kennedy pathway including:

i. *each of the biosynthetic steps,*
ii. *the functions and roles of the phospholipid products PC and PE, and*
iii. *how the Kennedy pathway has the potential of being a chemotherapeutic target against cancer and various infectious diseases. …*

Choline phospholipid metabolism is altered in a wide variety of human cancers. ***The observed elevated levels of phosphocholine are caused in part to the growth factor-activated Ras and phosphatidylinositol 3-kinase (PI3K) signaling cascades that stimulate the initial enzyme of the choline branch of the Kennedy pathway, CK****. CKs have been found to be activated in malignant cells and tumors of the lung, colon, breast, prostate, cervix, and ovaries.*

For this reason, it has been proposed to use CK as a prognostic marker for cancer progression as well as a molecular target for the development of novel cancer chemotherapeutic agents*. Toward this goal, the use of small interfering RNA or small hairpin RNA plasmids of CK has been shown to reduce intracellular phosphocholine, selectively reduces proliferation, and increases apoptosis in breast adenocarcinoma cells, but not in normal human mammary epithelial cells.*

Returning to Moessinger et al we note:

Lipids are stored within cells in lipid droplets (LDs). They consist of a core of neutral lipids surrounded by a monolayer of phospholipids, predominantly phosphatidylcholine (PC). LDs are very dynamic and can rapidly change in size upon lipid uptake or release. These dynamics require a fast adaptation of LD surface. We have recently shown that two Lands cycle PC synthesizing enzymes, LPCAT1 and LPCAT2 can localize to the LD surface….

The major phospholipid of the LD surface, phosphatidylcholine, can be synthesized by three different pathways:

(i) the de-novo pathway, which is also known as ***Kennedy pathway****,*

(ii) the Lands cycle and

(iii) the phosphatidylethanolamine methyl transferase (PEMT) pathway, which is restricted to liver cells.

In the Kennedy pathway, phosphocholine is activated with cytidine triphosphate (CTP) and transferred to diacylglyceride (DAG) to form PC*. These reactions are catalyzed by the cytoplasmic CTP:phosphocholine cytidylyltransferase (CT alpha) and the membrane-embedded cholinephosphotransferase or choline/ethanolamine phosphotransferase (CEPT1/CPT1).*

In the Lands cycle *phospholipase A2 (PLA2) removes fatty acids at the sn-2 position of PC, which results in the formation of lysophosphatidylcholine (LPC). This can be used in a reverse reaction, the addition of a fatty acid at the sn-2 position, to yield PC. This re-acylation is catalyzed by lysophosphatidylcholine acyltransferases LPCATs). Recently, four LPCATs were cloned and characterized.*

They are all reported to localize to the ER compartment. Due to their structure they divide into two subgroups with LPCAT1 and LPCAT2 in one *and LPCAT3 and LPCAT4 in the other group. LPCAT1 is reported to function in lung surfactant production, while LPCAT2 seems to be important in inflammatory reactions.*

Overall a great deal is known about PC and the LPCAT1 interaction. However, as we shall note, the specific details of this complex process is still missing.

3 OBSERVATIONS

We can now make several observations. Our interest is setting forth questions more than conclusions.

3.1 WHAT ARE THE MECHANISMS WHEREBY THE LC ENABLE AGGRESSIVE RECEPTOR ACTIVATION?

The presentations noted above reflect a reasonable set of observations and reflections on possible therapeutic targets. What seems to be missing are the details associated with this process. For example, we know that PC is produced but we do not know the details as to how this reflects in the activation of more growth factor receptors or others similar effects.

3.2 WHAT IS THE BEST THERAPEUTIC TARGET?

What is the proposed target? Is it LPCAT1 itself and if so how can it be targeted? What activates LPCAT1, and is it activated through one of the many kinase paths in the cells. Are there cell surface markers that show such activation?

3.3 WHAT MARKERS CAN OR SHOULD BE TARGETED TO ASSESS PROGNOSIS?

In many cancers one can now find multiple markers, often blood borne, to be used for diagnosis and prognosis. The question here is; are there any such markers here? One may ask if there are exosomes that contain such markers.

3.4 WHAT DRIVES THE EXCESS ACTIVATION OF LPCAT1?

It appears from the analysis that the "sole" factor is excess LPCAT1. However, what is driving that excess? The underlying gene is in overdrive in expression. Are there certain activation via growth factors or other activators or is the activation internal? If the latter then what is the genetic mechanism of this overdrive?

3.5 IS THERE ANY DRIVER BASED ON A STEM CELL ACTIVATION?

We know that many cancers have as a drive a stem cell[8]. Is the LPCAT1 a factor in the stem cell or all the cells.

[8] https://www.researchgate.net/publication/301542243_Cancer_Stem_Cells_and_Cancer_of_Origin_Redux

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