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1-carbon cycle metabolites methylate their way to fatty liver

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Abstract

Fatty liver is a complex disease often accompanying metabolic syndrome and Type II diabetes. Hepatosteatosis may have roots in multiple metabolic abnormalities. However, metabolic dysfunction in the 1-carbon cycle (1CC), which produces the methyl donor s-adenosylmethionine (SAM) and phosphatidylcholine (PC), induces hepatic lipogenesis in model systems. Human diseases where the 1CC or PC synthesis is disrupted, such as alcoholism, congenital lipodistropy or cystic fibrosis, often present with fatty liver. Because the 1CC is clearly linked to this disease, it is critical to understand how the individual metabolites drive mechanisms increasing stored hepatic lipids. This review summarizes evidence that ties the 1CC to fatty liver disease along with data proposing mechanisms for increased lipogenesis or decreased lipid export by phosphatidylcholine.

Keywords

1-carbon cycle; Methylation; Phosphatidylcholine; Fatty liver

Introduction

Lipid accumulation in metabolic disease is not just a problem in adipose tissue. Excess fat in the liver (hepatosteatosis) also contributes to metabolic dysfunction, contributing to the insulin resistance that leads to Type II diabetes [1]. Fatty liver occurs in multiple human syndromes, from alcoholic or non-alcoholic fatty liver disease (ALD or NAFLD) [2, 3] and also can be present in cystic fibrosis patients [4], those fed intravenously [5], or in patients with genetic lipodystrophy [6]. While the physiological roots of fatty liver are not completely understood, there is a clear connection to the 1-carbon or folate cycle (1CC), because mutations or drugs affecting key enzymes result in hepatosteatosis [7].

The 1CC falls at the crossroad of several anabolic processes producing amino acids, nucleotides, the redox protector glutathione (GSH) and the methyl donor s-adenosylmethionine (Figure 1, Table 1) [8]. Folate, a B-vitamin produced by microbiota and obtained through the diet, enters the first stage of the cycle, which can progress toward purine production or produce methionine. In the next part of the cycle, this methionine is converted to s-adenosylmethionine (SAM), the donor for nucleic acid, protein and

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phospholipid methylation. The product of these methyltransferase reactions, s-adenosylhomocysteine (SAH), is recycled back to methionine through homocysteine (Hcy) [9]. Another B vitamin, B_{12}, can be used in this regenerative process [9]. Hcy itself can also be converted to glutathione through the transsulfuration process [9]. Multiple aspects of the 1CC, such as glutathione generation or SAM-dependent DNA or histone modification, could contribute to the overall pathology of fatty liver disease, however, the 1CC metabolite with the most direct link to the initial lipid accumulation is phosphatidylcholine (PC) [10]. PC can be also produced *de novo* through the Kennedy pathway, independent of the 1CC [11]. In mammals, PC species generated by methylation differ in side chains from those produced by the Kennedy pathway [12]. In liver cells, where the demand for PC is high, as much as 40% of the SAM goes to PC production as phosphatidylethanolamine (PE) undergoes three sequential modifications by PE methyltransferase (PEMT) [12]. Thus, limitations in the 1CC in liver can have a profound effect on PC production. While PC production is associated with hepatic lipid accumulation in multiple human diseases, animal models and culture systems [10], a complete mechanistic picture of how decreased PC drives lipid production is not yet clear.

The 1CC, PC levels and fatty liver in human disease

The link between metabolic pathways tied to methylation and fatty liver disease was noted in the 1930s, when Dr. Vincent du Vigneaud found that rodents fed a diet deficient in methyl groups developed fatty liver [13]. Currently, both alcoholic and non-alcoholic steatosis have well defined links to the 1CC [8, 14]. Alcohol consumption challenges 1CC function at multiple levels. First, ethanol inhibits expression of key enzymes in the pathway [15], reducing functional output of the 1CC. Second, dietary folates are often not ingested at recommended levels, folate adsorption/storage is decreased and excretory output is increased [15]. Dietary supplementation with betaine or SAM have been proposed as therapeutic interventions in this disease [15].

The development of NAFLD is complex and incompletely understood. Considered to be the hepatic lesion in metabolic syndrome, hepatic steatosis along side decreases in response to circulating insulin [15]. Several genome wide association studies (GWAS) have also linked hepatosteatosis to 1CC or PC synthesis to human patients with fatty liver [16]. First, a variant of PEMT has been linked to fatty liver development in two GWAS studies [17, 18], although a linkage was not found in the Dallas Heart Study [19]. Second, methylene tetrahydrofolate reductase (MTHFR) has also been associated with fatty liver [16]. Finally, mutations in the rate-limiting enzyme for PC synthesis from the Kennedy pathway (phosphate cytidylyltransferase 1, *PCYT1*) have also been identified in two patients suffering from congenital lipodystrophy and fatty liver disease [20]. In an elegant study, the authors found that the mutated *PCYT1* alleles were expressed at low levels in patient-derived cells and that PC synthesis was reduced. Next, corresponding mutations were used in functional studies, where one allele was shown to be deficient in association with lipid droplet membranes [20]. While multiple metabolic pathways impact the full spectrum of phenotypes altered in fatty liver disease, there are clear links of 1CC and PC production that contribute to lipid accumulation in human liver.

The 1CC, Low-PC and lipid accumulation in animal models

Murine models

Hepatic lipid accumulation is a common phenotype in mice with targeted deletions in enzymes acting in the 1CC and also in mice with lesions in methylation-independent PC synthetic enzymes. Hepatosteatosis also correlates with dietary limitation in the 1CC [13] and reduction in expression of 1CC genes [21]. For example, an early study by Rinella and Green showed that a methionine-choline deficient (MCD) diet was associated with lipid accumulation in the liver and subsequent acquisition of inflammatory markers [22]. The MCD diet was also shown to exacerbate development of ALD in a porcine model [23]. Subsequently, Lu and colleagues published a seminal paper linking the 1CC and fatty liver. Targeted deletion of methionine adenosyltransferase 1A (*MAT1A)*, a SAM synthase expressed predominately in the liver, resulted in mice that accumulated fat in their livers which progressed to non-alcoholic steatohepatis (NASH), then hepatocarcinoma [24]. This progression occurred more rapidly when the animals were fed a choline deficient diet [24]. As would be expected for mice with deficiencies in SAM production, the ratio of PC to PE was significantly reduced in these animals [25]. Mutations in other 1CC enzymes upstream of SAM production are associated with fatty liver. *MTHFR* deficiency increases lipid accumulation in murine livers [26]. Interestingly, fatty liver was reduced in mice fed betaine, a 1CC metabolite that can also serve as a source for SAM in mammals [26]. Deletion of the betaine producing enzyme, (*BHMT*, betaine hydroxymetyl transferase) also reduces SAM and PC, induces fatty liver and leads to hepatocellular carcinoma [27]. Glycine n-methyltransferase (GNMT) is a SAM-utilizing enzyme that may serve as a “sink” for excess methyl donors [28]. Perturbing 1CC function through this pathway also induces steatosis (21), although in this case PC is increased and contributes to excess stored lipid (25). Finally, excess dietary folate has also been recently shown to reduce SAM and PC levels along with hepatic steatosis through feedback inhibition of MTHFR activity [29]. Thus, interference with 1CC function upstream of SAM is tightly correlated with lowered PC levels and development of fatty liver disease.

If PC production was a nexus for driving hepatic lipid accumulation, fatty liver should also occur in models where synthesis is directly inhibited. Indeed interference with PC levels through methylation-dependent or independent synthesis pathways results in hepatic lipid accumulation (reviewed in [11, 30]). As mentioned above, PC is linked to the 1CC through the activity of *PEMT* which uses SAM in three sequential methylation reactions to produce PC from PE [11]. As methyl-dependent PC production is predominant in the liver, whole body *PEMT* knockouts can be used to study physiological roles in mice. However, phenotypes of the *PEMT* −/− mice were complex. First, synthesis through the Kennedy pathway compensated for PC production on a chow diet [12]. Challenge of these animals with a choline-deficient diet, on the other hand, led to hepatic lipid accumulation and rapid liver failure [12].

PC synthesis through the Kennedy pathway is essential for viability; mice lacking the rate-limiting enzyme Choline-phosphate cytidylyltransferase A (*PCYT1a*, also known as *CCT/CTa*) die early in embryonic development [31]. However, mice with tissue specific deletions

in *PCYT1a* also accumulate liver lipids. Jacobs, et al. created a liver specific knockout of *PCYT1a* and found that although PEMT-dependent PC production increased 2-fold, PC also decreased while TAGs increased [31]. Thus, both direct blocks in PC synthesis or decreases in PC downstream of effects on SAM and 1CC function have a profound connection to lipid accumulation in mouse models of liver disease.

The 1CC may also be connected to lipid accumulation in adipocytes through alternative mechanisms. Kahn and colleagues have identified changes in several metabolites linked to the 1CC in white adipose tissue (WAT) from obese mice. They found that utilization of SAM by the enzyme nicotinamide n-methyltransferase (NMNT) impacts polyamine metabolism. Synthesis of polyamines, which are important for energy metabolism, also consumes SAM and their levels fall as NMNT uses available methyl donors [32]. The authors showed that reduction of NMNT in WAT and hepatic tissue increased energy expenditure in obese mice as SAM levels increased and polyamine synthesis recovered [32].

Invertebrate models

Interactions between the 1CC, PC and lipogenesis have also been intensely studied in invertebrate models, where genetic screens or other unbiased tools have greatly contributed to our understanding. In a groundbreaking study, Guo, et al performed a siRNA screen in Drosophila S2 cells for modulators of lipid droplet formation and classified results according to their size and morphology [33]. From this screen, PC biogenesis enzymes were identified as key players in the formation of large lipid droplets, along with genes with important roles in lipogenesis (*Drosophila melanogaster* SREBP) and those that were later shown to have important mechanistic roles in lipid droplet formation (ARF1/COP 1 components) [33].

Caenorhabditis elegans has also proved to be an important model for understanding links between the 1CC and lipogenesis, although two aspects of the mammalian pathway are incompletely conserved. First, methylation steps producing PC occur earlier in the pathway, converting phospho-ethanolamine to phospho-choline, as in plants [34]. Second, *C. elegans* appears to lack a BHMT ortholog, suggesting that choline can not be used as a methyl donor [35] and would only contribute to PC synthesis through the Kennedy pathway. However, blocking the 1CC through inactivation of the SAM synthase *sams-1* or interfering directly with PC production by RNAi of the phospho-ethanolamine methyltransferase *pmt-1* or *pmt-2* have clear effects on lipogenesis; increasing visible lipid droplets and stored TAGs which can be readily rescued when the Kennedy pathway is supported through dietary choline [36]. Interestingly, *C. elegans* must synthesize all the PC necessary for growth and reproduction, as the laboratory food source, E. coli, lacks this membrane phospholipid [37]. The ability to use unbiased genetic screens in *Drosophila* and *C. elegans* has enhanced our understanding of mechanisms inducing lipid accumulation when the 1CC is dysfunctional.

Mechanisms of low-PC action on lipogenesis: PC itself or downstream metabolites?

Metabolites are small molecules that are modified and assembled to build the components of the cell. Their levels may also influence activity of the molecular machines that transcribe

genes, respond to growth factors or control intra-cellular transport [38]. However, it can be quite difficult to describe the molecular mechanisms tying an abundant metabolite to a specific cellular process. This question is critical, as understanding the underlying molecular mechanism is key to designing therapeutics. However, metabolites are not amenable to the traditional structure:function studies used to determine mechanistic relationships between proteins. Furthermore, metabolites such as lipids have many different molecular species, depending on which side chains are added and how they are modified. Thus, determining which molecular processes are directly affected by metabolite levels and not a downstream or indirect consequence is difficult [39]. In the case of connections between the 1CC and lipogenesis the two metabolites more closely correlated with hepatic lipid accumulation, SAM and PC, could both affect a variety of mechanisms driving lipogenesis (Figure 2). As the major methyl donor, SAM has the potential to change gene expression through histone or DNA methylation [38, 40]. Many reports cite such alterations [7, 14, 15, 41, 42]. However, it is difficult to show which changes are sufficient to cause the lipid accumulation, although histone or DNA modification could contribute to lipogenic phenotypes driven by other mechanisms. Blocking PC synthesis from the 1CC or independently though the Kennedy pathway both cause fatty liver, suggesting that low-PC is sufficient to drive hepatic lipogenesis [10]. Nevertheless, whether it is PC itself or a downstream metabolite that exerts these effects, or which cellular pathways are impacted to drive lipogeneis, is incompletely understood.

As a structural component of cellular membranes, metabolic precursor to other lipids, a substrate for phospholipases and a ligand for nuclear hormone receptors, PC levels could impact diverse cellular mechanisms [30]. Early studies suggested that reductions in dietary methionine or choline affected secretion of lipoprotein particles such as VLDL [11]. Later murine models targeting PC production through the Kennedy pathway [31] or through methylation of PE [43] found that VLDL secretion decreased in both cases, trapping lipoprotein particles loaded with TAG in the liver. The authors showed in a separate study that VLDL particles had abnormally low PC/PE ratios and observed degradation in a post-endoplasmic reticulum compartment [44]. However, it was not clear low PC effects were due to incomplete membrane formation in the lipoprotein-particles, or if it could also affect signaling components controlling secretory processes.

Recent invertebrate studies have provided additional mechanisms that could increase the potential for hepatic lipid storage when the 1CC or PC production is limited. Using *C. elegans*, it was recently shown that animals with a knockdown in the SAM synthase *sams-1* contained large lipid droplets in the intestine [36] (which serves both endocrine and digestive functions) [45]. This increase in stored fat was driven by the transcription factor Sterol regulatory element binding protein (SBP-1/SREBP-1) [36], a master regulator of genes required for lipogenesis [46] and importantly, this regulatory circuit was conserved in mammals [36]. The SREBP family of transcription factors can be regulated at the transcriptional levels by insulin signaling or Peroxisome proliferator-activated receptor gamma (PPARγ) regulation, activated by proteolytic processing in a feedback loop responding to low cholesterol, and modified by phosphorylation, acetylation or ubiquitination during the transcription cycle [47]. Newly translated SREBPs are stored in the endoplasmic reticulum (ER) as intrinsic membrane proteins [47]. When cholesterol levels

drop, chaperones escort SREBPs to the Golgi where proteases release the N-terminal transcriptionally active domain [36]. Importantly, SREBP-1c overexpression is sufficient to induce fatty liver in murine models [48, 49]. It was found that when PC was low, mRNA levels of *sbp-1* (in *C. elegans*) or *Srebf1* (in mouse liver) did not increase, however, more of the active transcription factor entered the nucleus due to increased proteolytic processing [36]. When the rate limiting enzyme for PC production, *PCTY1* was knocked down by RNAi in HepG2 cells, Golgi-resident proteins such as the SREBP-activating proteases, assumed an ER-like pattern, allowing SREBP-1 maturation without transit to the Golgi [36]. While these studies uncovered important details of the mechanism, they did not reveal how the mis-localization of Golgi proteins occurred or what might link PC to this process.

Changes in PC levels in the ER or Golgi could have structural effects, altering membrane-bending properties, availability for synthesis of downstream lipids or phospholipase-dependent signaling cascades. While it was difficult to directly target PC to identify mechanistic links, proteins whose activity could be changed by membrane properties or PC availability could be analyzed. An RNAi screen in *C. elegans* identified factors that were necessary and sufficient for low-PC activation of SBP-1/SREBP-1 and determined which of these candidates was also relevant to low-PC processing in mammals [50]. Interestingly, it was found that depletion of *lpin-1*/LPIN1 and *arf-1.2*/ARF1 was sufficient to activate SBP-1 in *C. elegans* or SREBP-1 in mammalian liver-derived cells. Lipin 1 is a phosphatidic acid phosphatase that produces the diacylglycerol (DAG) used in triacylglycerol (TAG) and PC synthesis [51]. ADP-ribosylation factor 1 (ARF1) is a GTPase critical for Golgi-ER traffic, whose activation and cycling require membrane association [52]. Guo, et al. also identified *Drosophila* ARF in the S2 cell screen for lipid droplet modifiers [33], and subsequent work from the Walther and Farese labs found that ARF1 itself had an important role in lipid droplet formation [53]. Interestingly, in mammalian cells, the levels of active GTP-bound ARF1 were decreased in cells treated with siRNA to *Lipin 1* or *PCYT1*, which may be due to decreases in association of the ARF-GEF, GBF1 to these membranes [50]. Supporting the idea that levels of multiple lipids in PC synthesis pathways were disrupted, microsomal membranes from *sams-1* or *lpin-1(RNAi)* animals were shown to have altered lipid profiles; showing a relative increase of some PA species to PC [50]. This suggests that the mechanistic effects of low-PC occur upstream, as changes in PA, DAG and PC limit ARF-GTPase cycling and disrupt COP I transport. Thus, defects in 1CC function or PC production appear to change membrane properties allowing for activation of SBP-1/SREBP-1. SBP-1/SREBP-1 activation is an important part of a lipogenic program that could contribute to lipid storage as fatty liver develops.

SREBPs are important regulators of lipogenic gene expression, however, other transcription factors also regulate lipogenic genes and may be affected by PC through distinct mechanisms. Nuclear hormone receptors, such as liver-receptor homolog-1 (LRH-1), are intracellular receptors that become active transcriptional regulators upon ligand binding [54]. NHRs may bind a variety of ligands, however, two NHRs that can act in the liver have been shown to bind specific PC species. PPARα has a well established role as a regulator of fatty acid oxidation, lipid transport and gluconeogenesis [55] and it is the target of therapeutics [56]. The Semenkovich lab used tandem mass spectrometry to identify endogenous ligands for PPARα in the mouse liver and found that a specific species of phosphatidylcholine

(16:0/18:1 GPC) was associated with the active transcription factor [57]. Generation of this ligand required not only fatty acid synthase (FAS), but also the intact Kennedy pathway, demonstrating that PC synthesis was required. As impairment of PPARα reduces β-oxidation and shifts the cell toward stored energy [57], thus reduced levels of this ligand could also contribute to hepatic lipid storage.

Liver receptor homolog-1 (LRH-1) is important for controlling lipid levels in the liver and has a complex relationship with the 1CC. LRH-1 activates genes involved in bile acid transport, and targeted deletion results in fatty liver in mice [58]. Moore and colleagues determined that a PC moiety with two saturated fatty acid side chains (dilauroyl phosphatidylcholine (DLPC)) could serve as a ligand for LRH-1, allowing activation of genes promoting bile acid flux [59]. Interestingly, the gene for SREBP-1c along with its target genes in fatty acid biogenesis, were also decreased. To investigate the protective effects of this PC species, the authors administered DLPC to mice on a high fat diet and found that insulin sensitivity was improved, serum glucose levels fell and hepatic lipids decreased [59]. Importantly, the authors showed that these effects did not occur in LRH-1 deficient mice. Structural studies in the Ortland lab have provided additional mechanistic insights into the relationship between DLPC and LRH-1 by determining the structures of the PC bound receptor [60]. They find that DLPC interacts with amino acids outside the classic ligand-binding pocket, and importantly, that ligand binding alters interactions between co-activators and co-repressors. Many nuclear hormone receptors are partially unfolded in the unbound state, and ligand binding allows additional intra-molecular interactions thus stabilizing the active structure [61]. However, Musille et al find that the phospholipid backbone bridges the intra-molecular interactions, stabilizing and activating the receptor [60]. Finally, they find that interaction with co-activator peptides are favored by the ligand bound receptor, but that a co-repressor (SMRT) can directly interact with the unbound receptor [60]. The detailed molecular mechanism in this study provides a powerful example of how a phosphatidylcholine moiety could change the potential to store lipids in the liver by switching a nuclear hormone receptor from inactive to an active state.

A recent study has shown that LRH-1 is also critical for the expression of 1CC genes, impacting development of hepatosteatosis on a methyl-donor depleted diet [62]. Wagner et al. find that LRH-1 deficient mice are protected from fatty liver on methionine-choline deficient diets and that decreases in SAM and PC occurring on these diets is blunted [62]. Furthermore, they find that LRH-1 is a direct transcriptional regulator of *Gnmt1* [62], an enzyme that consumes excess methyl groups and that LRH-1 binding sites were located in the promoters of many 1CC genes [63]. Thus, LRH-1 may be an important regulator of methyl donor levels in the liver. Lastly, the authors state that the ligand for LRH-1, DLPC, is not likely to be synthesized through the 1CC-PEMT pathway [62], suggesting that a feedback loop is not likely in this instance. However, LHR-1 represents an intriguing link between levels of 1CC metabolites and lipid accumulation in the liver.

Concluding Remarks and Future Perspectives

The 1CC has many roles in the cell, contributing to nucleotide synthesis, redox protection, histone/DNA methylation and phospholipid synthesis [8]. Changes in 1CC function are

strongly associated with hepatic lipid accumulation [11], however, understanding which 1CC metabolites affect this process and how they directly impact cellular mechanisms is only now emerging. Deciphering the molecular mechanisms driving the development of metabolic disease has the added challenge of determining how metabolites directly impact signaling and transcriptional mechanisms or organelle function. Studies examining 1CC function and lipogenesis have identified multiple mechanisms that may contribute to excess lipid storage in the liver when 1CC metabolites or PC are low, from control of nuclear hormone receptors essential for lipid export, to activation of transcription factors activating the program of *de novo* lipogenesis. It is critical to add more mechanistic details to these models, understand other physiological effects of 1CC dysfunction, and determine if these mechanisms act in concert or are sufficient to cause liver disease on their own. In this way, we can begin to understand how hepatosteatosis develops and how to develop new tools to treat it.

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Outstanding questions box

How do individual metabolites affect molecular mechanisms? In the case of lipids such as phosphatidylcholine, are primary effects through membrane structure, interaction of specific PC species with transcriptional regulators, or do affects come as levels of lipids derived from PC are altered? In the case of SAM, what changes in methylation are tightly linked to SAM levels? Furthermore, which changes in histone or DNA methylation are sufficient to alter expression of lipogenic genes?

Which physiological effects of PC are linked to overall changes in this class of lipids, or large groups of species, and which are due to changes in a few or single species?

What are the processes that regulate 1-carbon cycle production or PC levels? Are nutritional changes sufficient to alter SAM or PC levels in a physiologically relevant way? What environmental changes may also cause perturbation?

Trends Box

Low levels of 1-carbon cycle metabolites or the methylated phospholipid phosphatidylcholine (PC) accompany lipid accumulation in invertebrate models, rodent and human liver.

Levels of s-adenosylmethionine (SAM), the major methyl donor, and PC have the strongest links as effectors of fatty liver.

SAM-dependent DNA or histone methylation could have effects on gene expression.

Low PC can affect signaling controlling intracellular transport, activating the a lipogenic transcription factor (SREBP-1). In addition, specific PC isoforms are required for activation of a nuclear hormone receptor (LRH-1) that drives bile acid export from the liver.

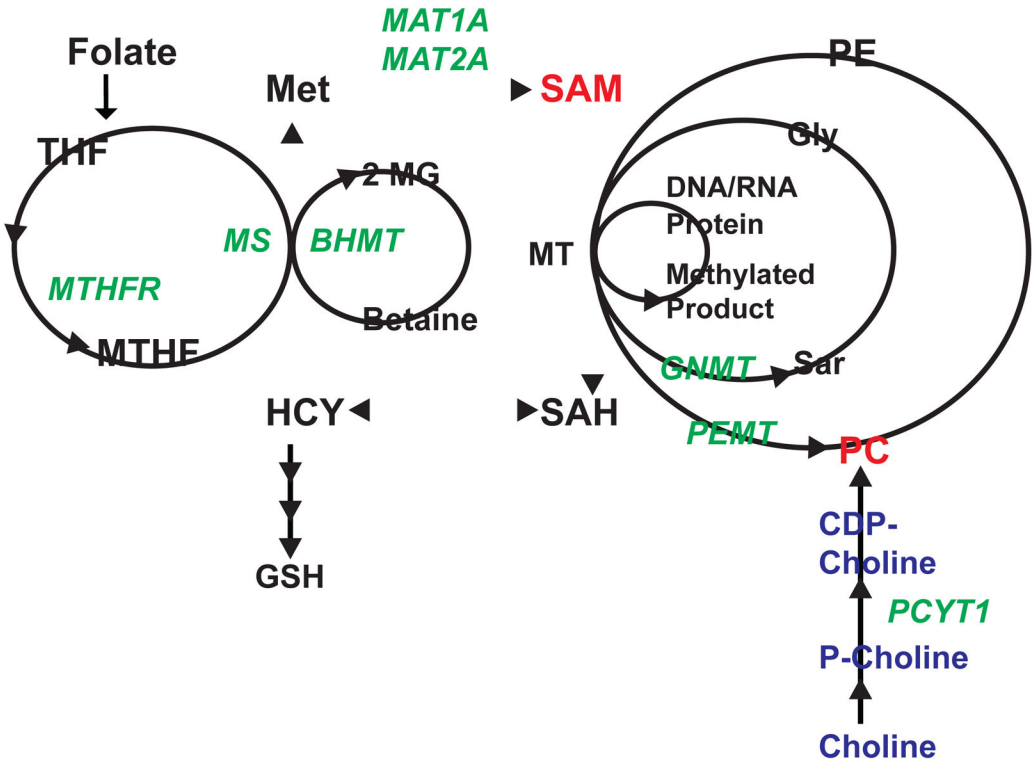

Figure 1. Schematic diagram of the 1CC

The 1-carbon cycle (1CC) consists of multiple interlocking pathways. Folate enters the cycle leading to MTFH (methyl tetrahydrofolate) conversion to methionine by MS (methionine synthase). Methionine is used to make SAM, which can be used by MTs to produce methylated proteins (including histones), nucleic acids, phosphatidylcholine (PC) or metabolites such as Sarcosine (Sar). The byproduct of these reactions, s-adenosylhomocysteine (SAH), can be used to regenerate methionine. Homocysteine (HCY), which is produced during the reconversion process, can also be diverted to Glutathione (GSH) production. Enzymes discussed in the text are in green, key metabolites in red. Enzymes: MTHFR (methyl tetrahydrofolate reductase), MS (methionine synthase), MAT (Methionine adenosyl transferase), BHMT (betaine hydroxy methyltransferase), GMNT (glycine n-methyltransferase), PEMT (phosphatidylethanolamine methyltransferase), PCYT1 (phosphocholine cytididyl transferase). Metabolites: THF (tetra-hydrofolate), MTHF (methyl tetra-hydrofolate), HCY (homocysteine), Met (methionine), GSH (glutathione), SAM (s-adosylmethionine), SAH (s-adenosyl homocysteine), PE (phosphatidylethanolamine), Gly (Glycine), Sar (Sarcosine), 2-MG (2-methyl glycine), MT (methyltransferase).

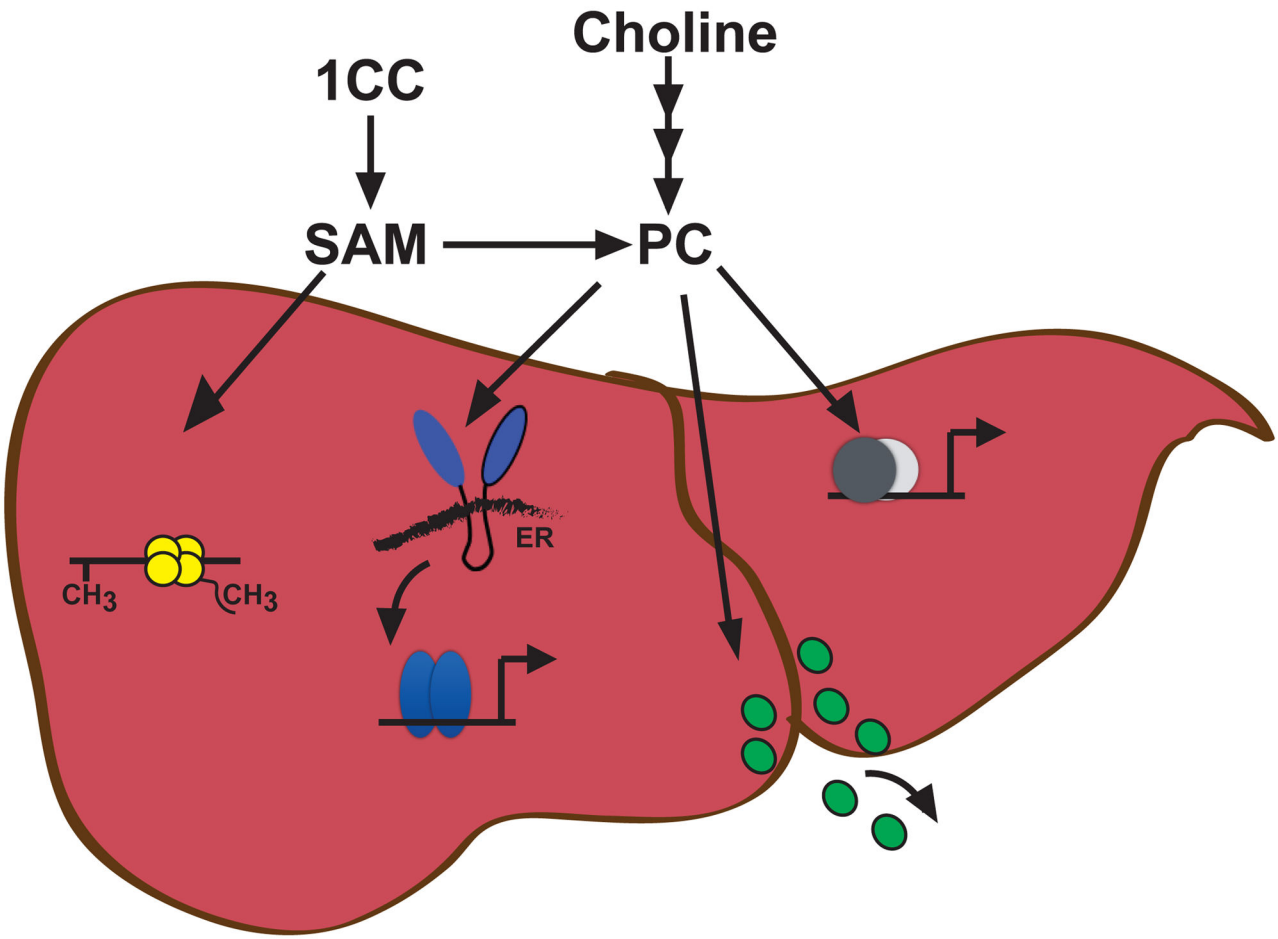

Figure 2: (Key Figure). Diagram illustrating pathways affected by low SAM or low PC that could lead to fatty liver

The 1CC (1-carbon cycle) has multiple links to lipid accumulation in the liver. SAM, the major methyl donor, can potentially directly affect gene expression if histone or DNA methylation patterns are sensitive to SAM levels. Furthermore, through changes phosphatidylcholine (PC) levels, activation of SREBP-1-dependent genes for lipogenesis or LHR-1 dependent genes for bile export could impact lipid accumulation in the liver. Finally, lower levels of PC could also limit export of lipoprotein particles, increasing total hepatic lipid levels.

1CC (1-Carbon Cycle), PC (phosphatidylcholine), LHR-1 (Liver homology receptor 1) SREBP-1 (sterol regulatory element binding protein -1), VLDL (very low density lipoprotein), LHR-1 (liver receptor homolog 1).

Table 1

Important metabolites, processes and physiological effects of the 1CC.

1CC metabolite	Process	System	Tissue	Ref
SAM	PC production	Human, Mouse C. *elegans, Drosophila*	Liver Liver Intestine S2 cells	[10]
	Spermidine production	Mouse	Liver Adipose	[32]
	Histone methylation	Human Mouse *C. elegans*	iPS cells, HCT116 cells Liver Intestine	[64–66]
	DNA methylation	Mouse	Schwann Cell	[67]
Methyl-tetrahydrofolate	Nucleotide synthesis			[68]