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Review article

The recent insights into the function of ACAT1: A possible anti-cancer therapeutic target

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ABSTRACT

Acetoacetyl-CoA thiolase also known as acetyl-CoA acetyltransferase (ACAT) corresponds to two enzymes, one cytosolic (ACAT2) and one mitochondrial (ACAT1), which is thought to catalyse reversible formation of acetoacetyl-CoA from two molecules of acetyl-CoA during ketogenesis and ketolysis respectively. In addition to this activity, ACAT1 is also involved in isoleucine degradation pathway. Deficiency of ACAT1 is an inherited metabolic disorder, which results from a defect in mitochondrial acetoacetyl-CoA thiolase activity and is clinically characterized with patients presenting ketoacidosis. In this review I discuss the recent findings, which unexpectedly expand the known functions of ACAT1, indicating a role for ACAT1 well beyond its classical activity. Indeed ACAT1 has recently been shown to possess an acetyltransferase activity capable of specifically acetylating Pyruvate DeHydrogenase (PDH), an enzyme involved in producing acetyl-CoA. ACAT1-dependent acetylation of PDH was shown to negatively regulate this enzyme with a consequence in Warburg effect and tumor growth. Finally, the elevated ACAT1 enzyme activity in diverse human cancer cell lines was recently reported. These important novel findings on ACAT1's function and expression in cancer cell proliferation point to ACAT1 as a potential new anti-cancer target.

1. Introduction

Acetyl-CoA acetyltransferase (ACAT) corresponds to two ubiquitous metabolic enzymes, which are respectively localized in the mitochondria and cytoplasm [1,2]. Mitochondrial acetyl-CoA acetyltransferase (ACAT1), a short-chain-length-specific thiolase known as acetoacetyl-CoA thiolase and 3-ketothiolase, catalyses the condensation of two acetyl-CoAs to make acetoacetyl-CoA as well as the reverse reaction, by breaking down acetoacetyl-CoA into two molecules of acetyl-CoA [3,4]. The direction of the above-mentioned reversible reaction toward making or breaking acetoacetyl-CoA depends on which pathway and tissue ACAT1 is involved [2,3].

The catalytic role of ACAT1 has been shown in isoleucine degradation, ketolysis, ketogenesis and fatty acid oxidation [3]. In the hepatic ketogenesis, ACAT1's function favours the formation of acetoacetyl-CoA, whereas in non-hepatic ketolysis ACAT1's activity tends to break down acetoacetyl-CoA [1,2]. Additionally ACAT1 is responsible for the reversible conversion of 2-methylacetoacetyl-CoA into propionyl-CoA and acetyl-CoA in isoleusine degradation pathway [3,5]. Over the past several years, ACAT1 deficiency as an autosomal recessive inherited metabolic disorder of isoleucine degradation and ketone body metabolism has been reported in multiple cases and was associated with a defect in mitochondrial acetoacetyl-CoA thiolase activity [6–10]. Patients diagnosed with ACAT1 deficiency show clinical symptoms such as ketoacidosis associated with vomiting and urinary excretion of 2-methyl-3-hydroxybutyrate, tiglylglycine and 2-methylacetoacetate [11]. It is therefore suggested that deficiency in ACAT1 activity essentially affects ketolysis [3,5,12]. Several mutations have been identified in the *ACAT1* gene and the inheritance of two copies of mutated *ACAT1* gene from parents causes ACAT1 deficiency in the child [13]. The clinical symptoms in affected individuals who are diagnosed early could be alleviated via dietary modifications including protein restrictions [14].

Very interestingly, recent studies shed light on the novel and unexpected functions of ACAT1, with a possible oncogenic role, which is the main focus of present review.

2. Mitochondria and cancer

One of the hallmarks of cancer is the deregulated metabolism [15]. Mitochondria are key organelles not only in cellular energy metabolism but also in modulating epigenetic landscape of the cell through providing metabolites such as acetyl-CoA, which serves as a substrate for histone acetyltransferases (HATs) to mediate reversible histone acetylation [16,17]. Mitochondrial enzymes are encoded by both mitochondrial DNA (mtDNA) and nuclear DNA (nDNA). Therefore the

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integrity and activity of mtDNA and nDNA as well as a coordinated expression of mitochondrial and genomic genes, are crucial for the normal function of the cells [18]. Cancer cells demonstrate a mutational defect in metabolic enzymes as well as a dysregulated expression level of mitochondrial enzymes. Increasing evidence supports the dependence of cancer cells on metabolic alterations. The metabolic switch from mitochondrial oxidative phosphorylation to aerobic glycolysis is suggested to be achieved through aberrant activity and/or expression of metabolic enzymes [19,20]. Elucidation of molecular mechanisms underlying metabolic alterations in cancer cells will have important therapeutic implications to target cancer cell metabolism. Identification and expanding the list of metabolic enzymes that their activity is altered under oncogenic signalling enhances the number of potential inhibitors that could be used in cancer therapy. For instance, mutation of genes encoding fumarate hydratase (FH), succinate dehydrogenase (SDH), isocitrate dehydrogenase (ISDH) has been reported in a variety of human cancers [21]. The ten-eleven translocation methylcytosine hydroxylases (TET) and the Jumonji C (Jmjc) histone demethylases are involved in demethylation of DNA and histones, respectively [22,23]. One of the required cofactors for these two enzymes is α-ketoglutarate (α-KG). The metabolites such as fumarate and succinate (the accumulation of these two metabolites occur due to the mutation in FH and SDH), which are structurally similar to α-KG, can inhibit the α-KG-dependent enzymes (TET and Jmjc) thus enhancing the levels of both DNA and histone methylation [24].

The involvement of metabolic enzymes in critical cellular functions is now becoming clearly demonstrated. As mentioned above, metabolic enzymes contribute to the epigenome programming through providing substrates such as acetyl-CoA and other metabolites that can be used by enzymes involved in “writing” the histone post-translational modifications (PTMs) [25]. These PTMs in turn could be “read” and “erased” and hence collectively control cellular gene expression [17,26,27].

PTMs not only affect histones but also a large variety of cellular proteins are modified by the metabolite-driven activities [17]. Among these proteins, post-translational modifications of metabolic enzymes have been reported to be critical in regulating their activity and hence in controlling the metabolic programs of the cell [28]. For instance, in the case of protein lysine acetylation, it has been shown that the activity of acetylated metabolic enzymes could be controlled through different mechanisms. In some cases, acetylation has been found to affect their catalytic activity and substrates accessibility. An example is lactate dehydrogenase A (LDHA) which convert pyruvate to lactate and is reported to be upregulated in many cancers [29]. Lysine 5 acetylation of LDH-A negatively regulate LDH-A activity and inhibits tumor growth. This negative regulation of K5-acetylated LDH-A is mediated via HSC70 chaperone which binds to K5-acetylated LDH-A and promotes its lysosomal degradation. Notably, increased levels of LDH-A and reduced levels of K5-acetylated LDH-A have been reported in the pancreatic cancer tissues compare to the normal tissues. The low level of K5-acetylated LDH-A observed in pancreatic cancer tissues may introduce LDH-A K5 acetylation as a potential marker of pancreatic cancer initiation [30].

Another example is PDC which is composed of three subunits, pyruvate dehydrogenase (E1), dihydrolipoyl transacetylase (E2) and dihydrolipoyl dehydrogenase (E3). The activity of PDC is controlled via phosphorylation/dephosphorylation of three serine residues of PDH (E1) catalysed by pyruvate dehydrogenase kinase (PDK) and pyruvate dehydrogenase phosphatase (PDP), respectively [31]. PDK facilitates phosphorylation of PDH, whereas PDP removes the inhibitory phosphate group [31]. It has been shown that the inhibition of PDC leads to the reduction of pyruvate to lactate known as lactagenesis, which is essential for cancer cell proliferation and tumor growth (Fig. 1) [32], therefore identification of upstream regulators of PDC can be very promising to target lactagenesis and consequently attenuate cancer cell proliferation. To this end, a recent study reported that ACAT1 acetylates PDC and inactivate its function which is the main focus of this minireview [33].

Acetylation can also control the amount and subcellular localization of metabolic enzymes [34]. In some cases, acetylation has been shown to activate a specific set of enzymes. For instance, acetylation of ATP-citrate lyase increases its stability due to a competition between acetylation and ubiquitylation for the same lysine residue [35]. To enable growth, cancer cells exhibit high glycolysis and lipogenesis. The elevated de novo lipid synthesis in cancer cells meets the demand of membrane biogenesis to promote tumor growth. ACLY is a key enzyme in de novo lipid synthesis and its upregulation has been reported in many cancers [36–38]. The recent study from Lin and colleagues showed that ACLY acetylation at lysines 540, 546 and 554 correlates with the enhanced ACLY protein levels and promotes cell proliferation as well as lipid synthesis. Interestingly, higher levels of K540, 546 and 554 acetylation was observed in lung cancer tissues compare to their adjacent normal tissues [35]. Altogether, these data brought insights into the post-transrational regulation of metabolic enzymes in cancer progression.

Besides this, recent evidences suggest that all the glycolytic enzymes, cytosolic enzymes such as ATP-citrate lyase and some of the mitochondrial enzymes involved in the Krebs cycle are translocated in the nucleus to regulate the state of chromatin marks and function [39–41]. For instance, in response to several signals such as mitochondrial stress, Epidermal growth factor (EGF) and oncogenic signalling, mitochondrial pyruvate dehydrogenase complex (PDC) is translocated in the nucleus to generate acetyl-CoA and cooperate with chromatin modifiers such as histone acetyltransferases to enhance histone acetylation and transcription of genes involved in the cell cycle progression and cell proliferation [39,42,43]. This link between metabolism and epigenetics enables cells to adapt to their environment either to fulfil their normal physiological functions or develop into pathological states [44].

Of note, mitochondria not only play a pivotal role in cancer development, progression but also in cancer chemoresistance. Most of the chemotherapeutic drugs stimulate apoptosis to eliminate tumor cells [45]. Mitochondria are at the heart of apoptosis regulation thus mitochondrial dysfunction could be involved in the resistance to apoptotic stimuli and could sustain the inability of cells to respond to cyto/genotoxic drugs [45,46].

3. The role of ACAT1 in cancer progression

Important recent studies identified the new function of ACAT1 and described how ACAT1 contributes to cancer biology by acting upstream of PDC to regulate its activity. In addition to its role in ketogenic pathway, isoleucine degradation and ketolysis, ACAT1 has also been recently reported to play roles in anti-cancer drug resistance, cancer cell proliferation and tumor growth [33,47,48]. However, the mechanisms underlying these activities remained to be defined. Consequently, several groups focused their attention on clarifying how ACAT1 contributes to promoting tumor growth. Saraon and colleagues analysed the transcript and protein expression levels of ketogenic-pathway-associated enzymes, including ACAT1, 3-hydroxy-3-methylglutaryl-CoA synthase 2 (HMGCS2), 3-hydroxymethyl-3-methylglutaryl-CoA lyase (HMGCL), D-beta-hydroxybutyrate dehydrogenase (BDH1) and succinyl-CoA:3-ketoacid-coenzyme A transferase 1 (OXCT1) in human prostate cancer tissues. They demonstrated that the expression of all the above-mentioned enzymes is elevated in high-grade compare to normal and low-grade prostate cancer tissues [49]. Additionally, Ue and colleagues, overexpressed ACAT1 in MDA-MB-231 breast cancer cells and showed its role in promoting tumor growth and metastasis, supporting the hypothesis that the key enzymes involved in ketone body re-utilization contribute to the tumor growth and metastasis [50]. Finally, Saraon and colleagues hypothesized that the over-expression of the above-mentioned ketogenic-pathway-associated enzymes in prostate cancer accelerates ketone body metabolism, which could be used as an

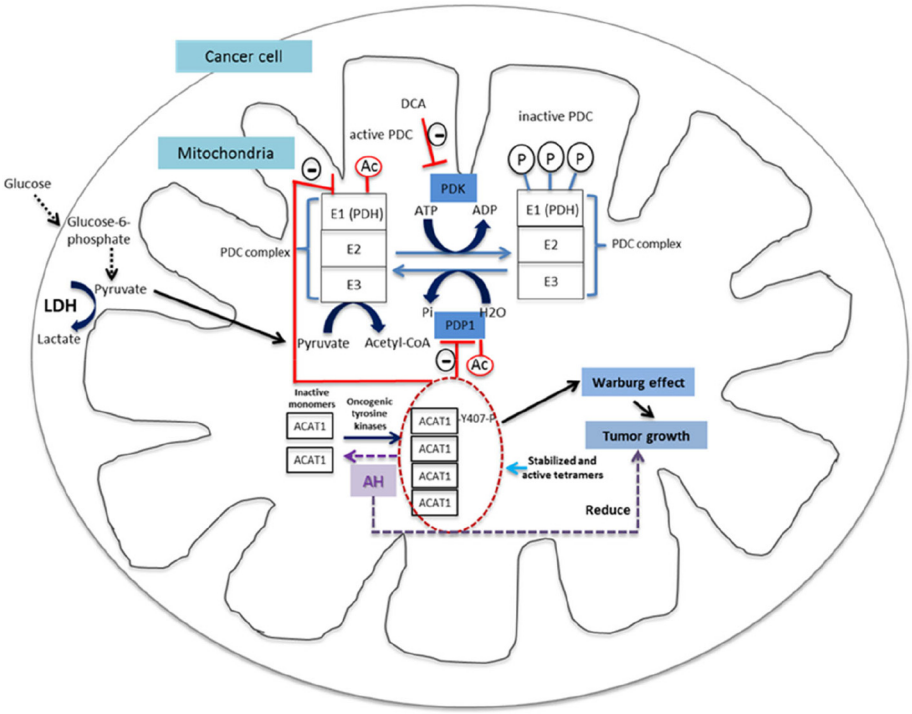

Fig. 1. Regulation of pyruvate dehydrogenase complex (PDC) activity by ACAT1 in cancer cells. Pyruvate dehydrogenase complex is regulated by phosphorylation and dephosphorylation by pyruvate dehydrogenase kinase (PDK) and pyruvate dehydrogenase phosphatase (PDP), respectively. Dichloroacetate (DCA) inhibits the PDK activity and sustains the PDC active. Irreversible decarboxylation of pyruvate to acetyl-CoA is catalysed by active PDC. Acetyl-CoA can then be oxidized via tricarboxylic acid cycle (TCA). Lactate dehydrogenase (LDH) converts pyruvate to lactate in the presence of phosphorylated PDC. Oncogenic tyrosine kinases such as EGFR, FGFR1, JAK2, FLT3 phosphorylates Y-407 and stabilize ACAT1 tetramer. Active ACAT1 tetramer acetylates PDP1 and PDH and exerts its inhibitory effect on PDC, which leads to lactate production and contribute to tumor growth through Warburg effect. Arecoline hydrobromide (AH) removes the inhibitory effect of ACAT1 on PDC and reduces tumor growth.
PDC; Pyruvate dehydrogenase complex, TCA; Tricarboxylic acid cycle, PDK; Pyruvate dehydrogenase, AH; Arecoline hydrobromide.

alternative energy producing pathway to nourish high energy demanding cancer cells [49]. Interestingly, ACAT1 has been also shown as a potential prognostic marker of prostate cancer [51].

Considering the important role of ketone body metabolizing enzymes in providing ATP for cancer cells [52], the inhibitors against these enzymes are of great interest as an anti-cancer therapeutic solution. With this respect, Fan and colleagues identified Arecoline hydrobromide (AH) from areca nut, the fruit of areca palm tree, as a natural ACAT1 inhibitor [33,53]. Ozsvari and colleagues performed in silico drug design and introduced new compounds to target mitochondrial ACAT1 and 3-Oxoacid CoA-Transferase 1 (OXCT1) and showed that these compounds can inhibit the proliferation of cancer stem cells (CSCs), which was not investigated for AH in Fan and colleagues' study [52].

Epigenetics mechanisms including DNA modification, histone post-translational modifications and non-coding RNAs regulate gene expression [54]. MicroRNAs are small non-coding RNAs (containing 19–23 nucleotides), which can bind to their complementary mRNAs and function as post-transcriptional regulator of gene expression [55]. miR-21 has been identified as an oncogene, which affects tumor growth, invasion and metastasis of breast cancer through negative regulation of several tumor suppressor genes such as programmed cell death 4 (PDC4), Tropomyosin (TPM1) and mapsin [56]. Several studies have shown that miR-21 level is up-regulated in a wide range of cancers [56–61].

Chanyshev and colleagues previously reported that the rat *ACAT1* gene is a target for miR-21 since the intraperitoneal injection of carcinogen compounds such as 1,1 trichloro-2,2-di (4-chlorophenyl) ethane (DDT) and benzo (a) pyrene (BP) to the female rats lowered the synthesis of miR-21 in the liver and subsequently enhanced the expression of its target genes including *Acat1*, *Armcx1* (Armadillo repeat-containing X-linked 1) and *Pten* [62]. In 2018, they examined the potential of miR-21 in targeting and regulating human *ACAT1* gene in MCF7 cells. They found that miR-21 targets 3′UTR of human ACAT1 mRNA. Next, they observed miR-21 down-regulated human ACAT1 and PTEN in MCF-7 cells and accelerated proliferation rate and inhibited apoptosis [63]. It is of note that this observation is in contrast with the reported effect of AH ACAT1-inhibited function on cell proliferation [33], which will be discussed in the section of Concluding remarks.

Besides promoting cancer initiation, several reports evidenced that mitochondria promote also chemoresistance [45]. A study by Lo and colleagues in 2015 aimed at enhancing the number of potential mitochondrial located proteins involved in resistance to anti-cancer drugs and at clarifying the molecular mechanisms involved. To this end, these authors carried out a mitochondrial proteomics study and found that ACAT1 and malate dehydrogenase 2 (MDH2) are overexpressed in doxorubicin-resistant uterine cancer cells and the knockdown of these two enzymes in MES-SA/DX-2 and MES-SA/DX-8 cells, sensitizes these cells to the doxorubicin treatment [48].

Interestingly several human cancer cell lines such as head and neck cancer, lung cancer and leukemia showed only upregulation in ACAT1 activity with no differences in the gene or protein expression in cancer cells compare to their corresponding normal cells [33]. In prostate cancer however, both elevated amounts of ACAT1 protein expression and activity were observed [33,51]. This observation encouraged scientists to investigate how ACAT1 activity is upregulated in diverse human cancer cells compared to normal proliferating cells. In this regard, Fan and colleagues used several approaches and shed light on how ACAT1 translates oncogenic signals to energy metabolism. Their findings demonstrate that ACAT1 exists as inactive monomers and active tetramers in the cells. Notably, phosphorylation of ACAT1 at tyrosine 407 (Y407) by oncogenic tyrosine kinases such as FGFR1, EGFR, FLT3, ABL1 and JAK2 stabilizes ACAT1 tetramers and enhances its activity (Fig. 1) [33].

With regards to tumor development, the next question raised was how activated ACAT1 contributes to cancer cell proliferation. Indeed cancer cell progression and tumor growth rely on altered cell metabolism and the Warburg effect is essential for the rapidly growing cancer cells [19]. As mentioned previously, PDC catalyses the oxidative decarboxylation of pyruvate to acetyl-CoA hence PDC deficiency results in Warburg effect [64]. It is well known that PDK and PDP regulate the activity of PDH [65,66]. Interestingly the results obtained by Fan and colleagues showed that ACAT1 acetylates PDHA1 and PDP1 through its acetyltransferase activity thus controls PDH function [33]. Acetylated PDHA1 and PDP1 in diverse human cancer cells inhibit the activity of PDH to promote glycolysis. Lysine acetylation of PDHA1 signals to

recruit PDK thus phosphorylates and inhibits PDC, whereas lysine acetylation of PDP1 sequesters it from PDH and stabilize the inhibitory phosphate group (Fig. 1) [33]. Notably, mitochondrial localized SIRT3 removes the acetyl moiety from acetylated PDHA1 and PDP1 thus activates PDC and exerts its anti Warburg effect to function as a tumor suppressor [67].

Taking into account the involvement of ACAT1 in tumor development, anti-cancer strategies based on the development of specific ACAT1 inhibitors appeared very promising. As discussed above, the Fan and colleagues have developed an inhibitor named AH, against ACAT1 to investigate whether targeting ACAT1 activity could slow down tumor development [33]. Interestingly, AH treatment of the human non-small cell lung carcinoma cell line H1299 and chronic myeloid leukemic cell line, K562 disrupted active ACAT1 tetramers, increased PDH activity and decreased lactate production. Moreover, H1299 xenograft in mice under AH treatment showed reduced tumor growth compared to non-treated control mice [33].

Altogether, the results of above-discussed studies point to ACAT1 as an oncogenic factor which promote the Warburg effect and tumor growth through acetylating PDHA and PDP1 in cancer cells. These findings raise the possibility that ACAT1 could directly or indirectly contribute to chromatin modifications in cancer cells (Fig. 2).

It is plausible that the oncogenic functions of ACAT1 include mechanisms beyond its ability to promote the Warburg effect via inhibiting PDC. Indeed, considering the reported moonlighting of cytoplasmic and mitochondrial metabolic enzymes in the nucleus [39] one could hypothesize that ACAT1 would also act in the nucleus. Such a mis-localized ACAT1 could act as a HAT and hence would contribute to the impaired levels of histone acetylation known to be associated with tumorigenesis [68]. It is possible that in cancer cells the highly expressed and active ACAT1 moonlights in the nucleus and takes advantage of its acetyltransferase activity to enhance histone acetylation.

Another hypothesis is that ACAT1 might also contribute to the histone hypoacetylation through inhibiting the function of mitochondrial PDC, which is known to translocate to the nucleus and promote histone acetylation by generating acetyl-CoA at the proximity of chromatin (Fig. 2).

Further studies using biochemical and in situ techniques are required to unravel the possible role of ACAT1 in the nucleus.

4. Concluding remarks

The investigation of ACAT1 in several types of cancer cell lines and tumor tissues evidenced the involvement of this ketogenic key enzyme in different aspects of cancer biology [33,48,50]. Several studies reported the deregulation of ACAT1 activity and expression in cancer cells compared to their normal counterparts [33,49]. The findings discussed in this minireview demonstrate that ACAT1 besides catalysing the reversible formation and breaking down of acetoacetyl-CoA, rewires cancer cell metabolism in response to oncogenic tyrosine kinases. In fact, ACAT1 possesses a lysine acetyltransferase activity by which acetylates pyruvate dehydrogenase (PDHA1) and pyruvate dehydrogenase phosphatase (PDP1) to inhibit PDC activity, therefore promoting Warburg effect and cancer cell proliferation. The stable and tetrameric form of ACAT1 enzyme, capable of acetylating PDHA1 and PDP1, is formed upon oncogenic tyrosine kinases activity. This mechanism explains very well how oncogenic signals inhibit PDC to regulate cancer cell metabolism and to promote Warburg effect [33,47]. Additionally, another work showed that overexpression of ACAT1 and MDH2 leads to chemoresistance to doxorubicine treatment of uterine cancer cells [48]. These important novel findings on ACAT1's function in cancer cell proliferation and chemoresistance point to ACAT1-PDH axis and tetrameric ACAT1 as potential new anti-cancer targets. In the search of ACAT1's inhibitor, Fan and colleagues identified AH as a natural ACAT1 inhibitor, which disrupts active ACAT1 tetramer to its inactive monomers and prevents its inhibitory action on PDH. AH can therefore be considered as an anti-cancer drug (Fig. 1) [33]. Additionally, miR-21 is elevated in many cancer types and has been shown to target human ACAT1 and PTEN [56,57,61]. Surprisingly, targeting ACAT1 by miR-21 mimic does not reduce proliferation. Indeed, both AH and miR-21 target ACAT1. miR-21 reduces ACAT1 level but compared to AH which inhibits ACAT1 activity, miR-21 exerts different effects toward cancer cell proliferation. The reason behind this observed contradiction and increasing cancer cell proliferation by miR-21

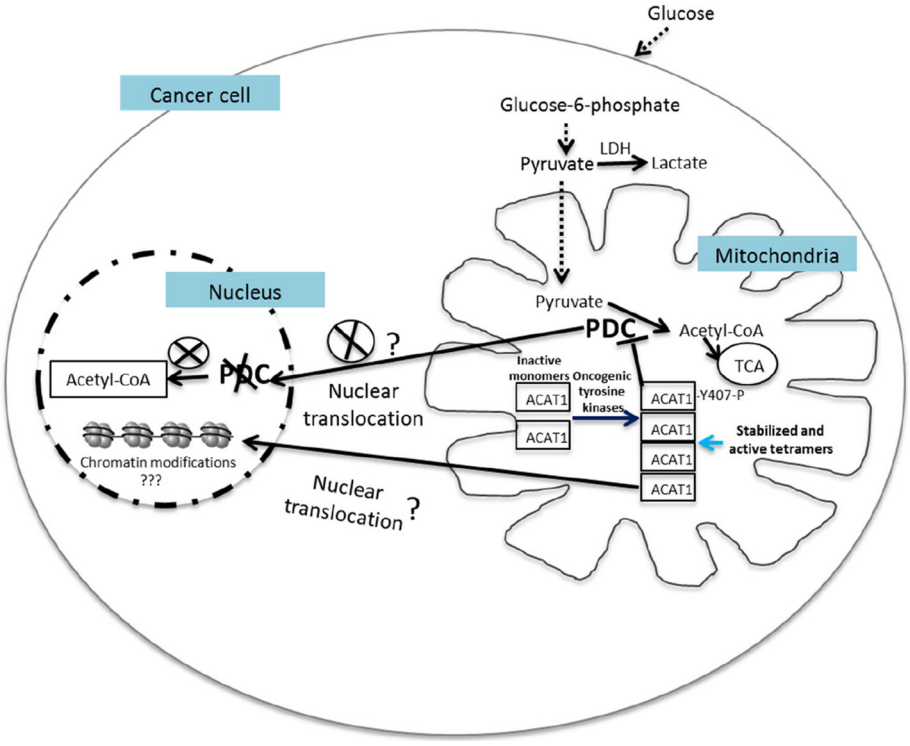

Fig. 2. The function of ACAT1 in cancer cells.
PDC is localized in the mitochondria and translocates in the nucleus to produce acetyl-CoA to drive histone acetylation. The elevated activity of ACAT1 in cancer cells inactivates PDC and results in lactagenesis. A question to address is how elevated activity of ACAT1 impacts chromatin modifications with regards to PDC translocation as well as the possible moonlighting of active ACAT1 in the nucleus.
PDC; Pyruvate dehydrogenase complex, TCA; Tricarboxylic acid cycle.

mimic is that miR-21 not only targets ACAT1 but also a variety of tumor suppressors including PTEN, hence leads to enhancement of cell proliferation which is not the case for AH [63].

In summary, recent investigations brought insights into the function of ACAT1 and in its ability to control PDC activity. To modulate the PDC activity, one could use either PDK or ACAT1 inhibitors, several PDK inhibitors such as dichloroacetate (DCA) and AZD7545 are in clinical trials. The question arises on what would be the differences of beneficial results for patients using either PDK or ACAT1 inhibitors (Fig. 1) [47].

The relevance of ACAT1 activity on the function of metabolic enzymes such as PDC requires further studies. It would be important to investigate how ACAT1 elevated activity impacts the state of chromatin marks with regard to PDC translocation into nucleus. Since ACAT1 sustains inactive and non-functional PDC in the mitochondria (Fig. 2). On the other hand, the presence of nuclear PDC in human cells has been evidenced thus both mitochondrial and nuclear PDCs are important for histone acetylation [42]. Although pyruvate dehydrogenase kinase (PDK) phosphorylates and inhibits mitochondrial PDC but it is not efficient to inhibit nuclear PDC since PDK is not present in the nucleus thus cannot impact on nuclear PDC activity. Taking into account this issue it would be interesting to investigate whether ACAT1 is present in the nucleus. Does ACAT1 impact on nuclear PDC too? If ACAT1 translocates to the nucleus what would be its effect on nuclear PDC associated histone acetylation? Do mitochondrial PDC and ACAT1 translocate to the nucleus simultaneously or individually? Do we have sometimes ACAT1 and sometimes PDC in the nucleus? Addressing all above-mentioned outstanding questions could unravel additional potential unknown functions of ACAT1.

Additionally, it would be important to further characterize other ACAT1's targets using proteome-wide approaches.

Answer to all these questions should undoubtedly depict a new picture of ACAT1 physiological and pathological activities.

Declaration of Competing Interest

There is no conflict of interest.

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