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REVIEW

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ACSS2 and metabolic diseases: from lipid metabolism to therapeutic target

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Abstract

Elevated incidence of metabolic disorders has been reported worldwide in the recent decade, highlighting the need for developing efficient therapies. These diseases result from a complex interplay of various factors that contribute to disease progression, complications, and resistance to current treatment options. Acetyl-CoA Synthetase Short Chain Family Member 2 (ACSS2) is a nucleo-cytosolic enzyme with both lipogenic and metabolic regulatory roles. Studies on ACSS2 have shown that it is involved in pathways commonly dysregulated in metabolic disorders, leading to fat deposition and disrupted cellular signaling. Although multiple studies have suggested a role of ACSS2 in the metabolic rewiring during tumorigenesis, few studies have examined its involvement in the pathophysiology of metabolic diseases. Recent evidence indicates that ACSS2 may contribute to the pathogenesis of various metabolic disorders making its examination of great interest and potentially aiding in the development of new therapeutic strategies. The objective of this review is to summarize the current understanding of ACSS2's role in metabolic disorders and its potential as a therapeutic target.

Keywords ACSS2, De novo lipogenesis, Diabetes, Obesity, Kidney injury, Liver diseases, Metabolic diseases

Search strategy

The data for this review was gathered by conducting a comprehensive search of the PubMed database for research articles published up to the present. The following keywords were used to identify relevant studies: ACSS2, ACS1, AceCS1, ACLY, metabolism, NAFLD, MAFLD, obesity, diabetes, and inflammation. Articles that discussed molecular and physiological roles of ACSS2 in relation to metabolic disorders were prioritized. The search strategy was refined to include studies exploring both mechanistic insights and therapeutic implications, ensuring a comprehensive review of current research in these areas. In addition, a targeted search was conducted on ClinicalTrials.gov to identify any clinical trials specifically investigating ACSS2. This search was aimed at assessing the development of potential new therapeutic approaches that target ACSS2 in metabolic disorders.

Introduction

Metabolic disorders are a common form of noncommunicable diseases (NCD) that are highly prevalent worldwide. They are characterized by a wide range of complications, making them a serious public health issue [1]. These diseases represent a spectrum which includes hypertension (HTN), diabetes mellitus (DM), hyperlipidemia (HLD), obesity, and Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD). They often occur together, sharing many common risk factors and

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complications, which can lead to premature death. Data from 2000 to 2019 showed elevated prevalence rates of all of these metabolic disorders, with the highest mortality reported in the Eastern Mediterranean region [1]. Given that metabolic disorders might greatly affect the lifespan of the patients, especially that their occurrence and hospitalization is increasing in alarming rates even in young adults, it is crucial to understand the pathophysiology of such diseases to develop efficient treatments.

Lipotoxicity, defined as the accumulation of lipids that disrupts normal cellular functioning, is considered a common causative factor for metabolic syndrome. For instance, overwhelming adipose cells with lipid accumulation is correlated with pancreatic β-cells decompensation. This leads to high plasma levels of fatty acids, a phenomenon known as hyperinsulinemia, which is associated with the development of metabolic disorders such as obesity and diabetes [2]. Similarly, multiple studies have reported that lipid metabolism disorders are associated with the development of MAFLD, further supporting the role of fatty acids in the pathogenesis of metabolic diseases [3]. Fatty acids are crucial molecules in organisms that participate in several metabolic processes including lipid synthesis and energy production. Their ligation to Coenzyme A (CoA) is required for activation, enabling their integration into various cellular pathways. A key player in acetyl-CoA production from citrate is ATP-citrate lyase (ACLY), which links glucose metabolism to lipid synthesis [4]. Acetyl-CoA can be derived from glucose, fatty acid catabolism, pyruvate, and branched-chain amino acids metabolism [5]. Initially, acetyl-CoA is produced within mitochondria, where it condenses with oxaloacetate to form citrate, subsequently entering the tricarboxylic acid (TCA) cycle. To make acetyl-CoA available in the cytosol and nucleus, citrate is exported from mitochondria through the citrate–malate shuttle. In the cytosol, ACLY cleaves citrate into acetyl-CoA and oxaloacetate, supplying acetyl-CoA for lipid biosynthesis, histone acetylation, and other cellular functions [5]. While ACLY is essential during embryogenesis, its inhibition in adult mammals can be tolerated due to an alternative pathway for acetyl-CoA production via Acetyl-CoA Synthetase Short-Chain family member 2 (ACSS2). ACSS2 is unique in its ability to produce acetyl-CoA by utilizing free acetate either exogenously from the cellular microenvironment or produced intracellularly from histone deacetylation, especially under low-energy or low-glucose conditions. In this way, ACSS2 supports metabolic flexibility, allowing cells to maintain acetyl-CoA levels when glucose availability is limited. The discovery of ACSS2 highlights the role of acetate as an alternative carbon source in acetyl-CoA production, complementing the glucose-derived pathway of ACLY [5, 6].

Acetyl-coenzyme A synthetases (ACSs) are enzymes that were first identified in yeast [7]. Then, upon examining the mammalian genes activated by sterol regulatory element binding proteins (SREBPs), subtractive hybridization identified three genes with sequence homology to the ACS gene of yeast. ACSs function in the conversion of acetate into acetyl-CoA, enabling the utilization of this substrate in various metabolic pathways [8]. Three members of the ACS family have been identified in the human genome ACSS1, ACSS2 and ACSS3 [9]. Studies have shown that both ACSS1 and ACSS2 mainly use acetate as a substrate, while ACSS3 has higher affinity and utilization of propionate [10, 11]. Studies on the different expression levels of the isoforms of the enzyme revealed that ACSS1 is highly present in the heart, skeletal muscle, and brown adipose tissue [12]. In contrast, ACSS2 is expressed in almost all of the studied tissues, with varying levels of expression. Notably, high expression levels of ACSS2 were found in the muscles, kidneys, small and large intestines, and adipose tissues; moderate expression levels were found in the lungs, liver, and brain; whereas the lowest levels were detected in bone marrow and lymph nodes [12]. Subcellular fractionation revealed that ACSS1 is a mitochondrial matrix enzyme functioning in the production of acetyl-CoA needed for energy production under ketogenic conditions via the citric acid cycle. On the other hand, ACSS2 appears to be a nucleo-cytosolic enzyme that functions in the cytosol and also translocates to the nucleus under stress conditions. Given that ACSS2 is found in various tissues, studies on its subcellular localization in each are limited. However, current studies show that ACSS2 is predominantly located in the cytosol of ganglion cells of the cranial nerves; while being a prominent nuclear component in other brain cells such as neuronal, astroglial and oligodendroglial cells. An increase in its expression level is observed upon stress, such as brain injury [12, 13].

While there is still no defined structure for ACSS2 in humans, it is suggested that the bacterial ACS is composed of 80% amino portion and 20% carboxy portion, with multiple conserved protein destabilization elements [14]. ACSS2 is found in various tissues and functions as a monomer to produce acetyl-CoA from acetate in an ATP-dependent reaction, providing the active form of acetate for lipid metabolism and energy production [15]. It is widely suggested that ACSS2 might also play a role in converting other short chain fatty acids (SCFA) to their active CoA ligated molecules (SCFA-CoA) such as converting butyrate and crotonate to butyryl-CoA and crotonyl-CoA respectively [16, 17]. Also, a recent article highlighted the role of ACSS2 in converting other substrates such as lactate, into lactyl-CoA which binds to lysine acetyltransferase 2 A (KAT2A) and lactylate histone H3. Consequently, Wnt/β-catenin, NF-κB, and

PD-L1 are activated leading to brain tumor growth and immune evasion [18]. However, a more recent study proposed the need to re-examine the role of ACSS2 in different SCFA conversions, as it was shown that ACSS2 efficiently converted acetate into acetyl-CoA in a hepatoblastoma cell line (HepG2), but was not able to generate SCFA-CoA from four carbon fatty acids such as butyrate and crotonate [19]. An explanation for this might be cell-type dependent, where ACSS2's function on different types of substrates could be influenced by the cell type or tissue origin. A closer examination of its roles in the tissues where it is expressed may provide a clearer understanding of its ability to convert different substrates into their active forms and, thus, their participation in subsequent cellular processes.

The regulation of ACSS2

ACSSs activity is primary regulated through reversible acetylation and deacetylation processes, where they are deactivated by acetylation. However, the deacetylases SIRT3 and SIRT1 can reactivate ACSS1 and ACSS2, respectively, by deacetylating their lysine residues, thereby enabling the conversion of free acetate into acetyl-CoA. This was demonstrated in experiments testing the effect of sirtuins on ACSS in cells, where overexpression of SIRT3 and SIRT1 reactivated the inactive, acetylated enzymes, as shown by the enhanced acetate incorporation and fatty acid synthesis [20]. Further evidence showed that ACSSs are also regulated by phosphorylation, which affects their cellular localization. Unphosphorylated ACSS2 is retained in the cytoplasm; however, under metabolic stress, ACSS2 phosphorylation exposes the nuclear localization signal (NLS), allowing ACSS2 to translocate into the nucleus–where it contributes to the activation of gene transcription [21]. This signifies that processes involved in the regulation of ACSS2 activity, represented by the deacetylation and phosphorylation epigenic modifications, are important for aiding the enzyme in the switching between its cytosolic and nuclear functions.

ACSS2's dual function

Examining the functions of ACSS2 revealed that it has a dual role, functioning as a lipogenic and a regulatory enzyme as well. ACSS2 was initially associated with lipid metabolism, where, upon cholesterol or fatty acid reduction, SREBPs -transcription factors regulating cholesterol and unsaturated fatty acid synthesis – are modified to produce active proteins that translocate to the nucleus and activate the expression of genes associated with lipogenesis, including ACSS2 [8]. This was further supported by experiments involving the knockout of *ACSS2* in mice fed with high fat diet (HFD), which have shown less fat deposition in the adipose tissue of $ACSS2^{-/-}$ mice compared to the wild type, reflecting the role of ACSS2 in lipid synthesis [22]. Moreover, a recent study revealed that hyperacetylated histones resulting from high fat content can be used as an alternative carbon source, serving as reservoirs for the generation of lipogenic acetyl-CoA. ACSS2 is the enzyme involved in converting acetate derived from the deacetylation of hyperacetylated histones into lipogenic acetyl-CoA, emphasizing ACSS2's role in acetyl-CoA generation and lipid synthesis [23].

ACSS2 is not only involved in lipogenesis, but it also has multiple identified regulatory roles. For instance, studies have shown that ACSS2, by regulating the acetyl-CoA levels, may also impact other processes such as autophagy. Knockdown of ACSS2 in cultured mammalian cells as well as mice, resulted in acetyl-CoA depletion, which decreased the cytosolic protein acetylation and induced autophagy [24]. Recent evidence revealed that ACSS2 also serves as a regulator for multiple transcription factors and pathways during well-fed physiological condition, as its loss leads to the dysregulation of several canonical pathways and cellular processes mainly in the liver, brain, and mesenteric adipose tissue [25]. Under conditions of stress, hypoxia, nutrient deprivation, or injury, ACSS2 translocate to the nucleus, facilitating the acetylation of multiple proteins, including histones and transcription factors such as the hypoxia-inducible factor 2 alpha (HIF-2α), thereby affecting gene transcription and metabolic reprogramming [21, 26]. This dual role supports ACSS2's characterization as a "task switching metabolic effector", transitioning from its cytoplasmic role in lipogenesis to an epigenic regulator in the nucleus affecting chromatin remodeling and gene transcription. Given the importance of the lipogenic and regulatory roles of ACSS2 in processes that help in maintaining cellular homeostasis and survival, dysregulation of ACSS2 has been studied in various diseases including cardiovascular disorders, obesity, diabetes, and cancer [25].

ACSS2 in cancer metabolism

One of the prominent examples that highlight ACSS2's role in pathophysiological processes is reported in cancer, where multiple studies have examined the different aspects of the enzyme's contribution to the tumorigenesis mechanisms and therapeutic potential, rendering it a better understood topic as opposed to ACSS2's role in other diseases [27–29]. This can be explained due to the presence of a metabolically challenged microenvironment which is a common hallmark of several types of cancer, characterized by decreased blood supply, which affects oxygen and nutrients availability. As a result, cancer cells develop additional mechanisms in order to survive in this stressful environment, such as using acetate as an additional carbon source [30]. Studies have shown that ACSS2, which is often upregulated in some tumors,

participates in the metabolic rewiring of tumor cells in order to maintain acetyl-CoA levels [31]. Thus, ACSS2's role in producing acetyl-CoA from acetate provides a growth advantage for cancerous cells. ACSS2 has been shown to be upregulated in around 40% of invasive ductal carcinomas [30]. Additionally, ACSS2 promotes the development of various cancer types, including brain cancer, breast cancer, melanoma and lung cancer [30, 32–34].

Consistent with its metabolic role, especially its activation under stress conditions such as hypoxia, and low serum or glucose availability, ACSS2 is believed to be involved in the survival of cancer cells by producing acetyl-CoA for signaling pathways or acting as an epigenetic regulator for protein acetylation [35, 36]. For instance, studies on renal cell carcinoma (RCC) have shown that cancerous cells have higher expression of ACSS2 compared to the normal cells, suggesting that ACSS2 acts as an oncogene promoting cancer cell proliferation, migration, and invasion. This was further demonstrated by showing that silencing ACSS2 inhibited PI3K/AKT pathway, a signaling pathway involved in tumor progression [37]. Moreover, studies reveal that under glucose limitation, acetate activates ACSS2, which then participates in the histone acetylation of SNAI1, one of the mediators of epithelial to mesenchymal transition, promoting RCC metastasis [35]. Similarly, the translocation of the phosphorylated ACSS2 to the nucleus has been shown to be important in transcribing genes related to lysosomal biogenesis, autophagy, cell survival, and the promotion of brain tumorigenesis [21].

Research on the role of ACSS2 in tumors is gradually increasing, with multiple recent studies further proving the contribution of ACSS2 to tumor progression processes. For instance, ACSS2 appeared to be an important molecule in the metabolic crosstalk between pancreatic cancer cells and stromal cells. Upon secretion of acetate by tumor-associated fibroblasts, ACSS2 allows its use for regulating cancer cells epigenome and transcriptional states. ACSS2 has a dual role, facilitating histone acetylation and enhancing the stability of specificity protein 1 (SP1), a transcription factor responsible for metabolic reprogramming under acidosis conditions. As a result, ACSS2 contributes to the expression of *SAT1* gene, regulating the secretion of polyamines required for essential cellular processes such as DNA replication, transcription, translation and cell cycle progression, thereby supporting cancer cell growth and survival [38].

Furthermore, the ability of cancer cells to alter their metabolic pathways and metabolite sources remains a challenge to metabolism-targeted treatment options. ACSS2 may enable cancer cells to resist such treatments. For example, Devimistat, a phase III clinical trial metabolic inhibitor, did not benefit acute myeloid leukemia (AML) patients due to the ability of the tumor cells to adapt by relying on another metabolite sources for survival. The inhibition of the Pyruvate Dehydrogenase (PDH) upon Devimistat administration leads to decreased glycolysis and compensatory reliance on gluconeogenesis. This adaptation is possible due to reliance on other acetyl-CoA sources, with ACLY and ACSS2 being the enzymes used for this purpose [39]. Similarly, ACSS2 can partially interfere with melanoma heterogeneity and stem cell therapy resistance. Research showed that the cancer stem cell marker aldehyde dehydrogenase 1A3 (ALDH1A3) forms an enzymatic complex with ACSS2, leading to changes in histone acetylation and thus the transcriptional states of cancer cells. Such modifications include high expression of glucose metabolism genes contributing to the resistance of melanoma cells to targeted therapies [40]. Thus, ACSS2 nucleo-cytosolic nature and dual function appears to be involved in the regulation of metabolic pathways that allow the progression of aggressive diseases such as cancer, complicating the responsiveness to available treatment options.

While previous studies strongly suggest that ACSS2 facilitates acetate utilization to promote various carcinogenesis mechanisms, other research indicates an opposite effect for acetate in certain cancer types. For instance, studies on glioblastoma cells, both in vitro and in vivo, demonstrate that acetate supplementation induces growth arrest rather than supporting tumor progression [41]. In these cases, the conversion of acetate into acetyl-CoA by ACSS2 facilitates histone acetylation of tumor suppressor genes, which are often silenced due to hypoacetylation in glioma [41]. These findings were validated using glyceryl triacetate (GTA) as an acetate source, tracking its effects on tumor development. ACSS2 was found to localize to the nucleus, functioning as an epigenetic regulator by increasing the acetylation of genes responsible for cell cycle regulation, ultimately leading to growth inhibition [41]. Similarly, another study demonstrated that GTA supplementation contributes to glioblastoma growth inhibition, not through inducing differentiation or apoptosis, but via the acetylation of cell cycle proteins. This further highlights the importance of epigenetic modifications in tumor suppression, initiated by the conversion of supplemented acetate into acetyl-CoA by enzymes such as ACSS2 [42]. Moreover, acetate supplementation appears to enhance the effectiveness of chemotherapy, making it a potential chemotherapeutic adjuvant when combined with temozolomide (TMZ) for treating glioma. This combination results in greater tumor reduction and improved survival rates [43]. Colon cancer provides another example where acetate supplementation yields mixed findings. A study indicates that acetate enhances colon cancer growth by activating the ACSS2/HIF-2 signaling pathway under hypoxic and

nutrient-deprived conditions [44]. Acetate supplementation was shown to promote cancer cell migration and invasion, as evidenced by augmented cancer growth in acetate-supplemented wild-type ACSS2 mice compared to ACSS2 knockdown mice [44]. Conversely, another study reports that acetate reduces proliferation of colon cancer cell lines under normoxic conditions by increasing oxygen consumption and reactive oxygen species (ROS) levels independently of ACSS2. However, under hypoxic conditions, ACSS2 expression and lipid levels increase, serving as a protective mechanism for cancer cells against acetate's anti-proliferative effects [45]. These mixed findings underscore the complex roles of acetate and ACSS2 in tumor progression or inhibition. The impact of ACSS2 on tumor cells likely depends on its interactions with other factors, highlighting the multifaceted pathways in which ACSS2 is involved.

This review underscores the potential contribution of ACSS2 to metabolic disorders. By synthesizing findings from various studies investigating the role of ACSS2 in different metabolic diseases, it offers a novel perspective by recognizing ACSS2 as a key player in conditions beyond cancer. While previous reviews have primarily focused on the involvement of ACSS2 in tumorigenesis, this paper expands the discussion to highlight its significant role in the manifestations of metabolic syndromes, an area that has received limited attention to date.

ACSS2 and metabolic disorders

Post translational modifications (PTMs) including phosphorylation, methylation, and acetylation are thought to be implicated in the progression of metabolic disorders, suggesting that targeting the enzymes that function in PTMs might be an effective therapeutic strategy for treating these conditions [46, 47]. Additionally, lipids are also associated with the development of metabolic syndrome manifestations in obese patients and play a role in MAFLD. This infers that fatty acids and fatty acids-related genes can also be therapeutic targets for treating metabolic disorders [48, 49].

Given the role of ACSS2 in several metabolic pathways, and consistent with its function in PTMs and in fatty acids metabolism, understanding the contribution of ACSS2 in the pathophysiology of metabolic disorders is of great interest and might lead to advances in finding suitable therapies. Although ACSS2 is proven to be involved in multiple pathways altered in metabolic disorders, such as de novo lipogenesis (DNL), fatty acid synthesis, and inflammatory responses, its role in the development and pathophysiology of these diseases is still not extensively explored.

This review presents a summary of the findings that consider the role of ACSS2 in the development of multiple metabolic diseases including hepatic steatosis, obesity, and diabetes (Table 1) highlighting the possibility of using ACSS2 as a therapeutic target for the treatment of such diseases (Fig. 1).

ACSS2 and hepatic steatosis

Dysregulation of lipid metabolism in the liver can be closely related to the development of multiple disorders, one of which is hepatic steatosis initially known as NAFLD [50]. A more recent and appropriate term for the disease is now recognized as Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD). This change aims to more accurately link liver diseases correlated and provide a more representative framework for understanding the disease process and its diagnostic criteria [51]. The disease can manifest as fat accumulation, known as nonalcoholic fatty liver (NAFL), or as nonalcoholic steatohepatitis (NASH), which is associated with tissue damage and inflammation. MAFLD often progresses toward fibrosis, cirrhosis, liver failure, and hepatocellular carcinoma [52, 53]. Studies examining the clinical manifestations of MAFLD have shown that the majority of patients are asymptomatic; however, upper abdominal pain, fatigue, thirst, and anxiety can be considered the most common symptoms [54]. Although the occurrence of MAFLD was reported to be mostly associated with other metabolic disorders, studies revealed that it can be also diagnosed in lean individuals, indicating the presence of underlying specific metabolic dysfunction leading to MAFLD [55, 56].

Many studies have attempted to understand the pathophysiology of MAFLD. However, it remains a complex elusive process. The most accepted hypothesis suggests that the development of the disease occurs as a two-step process. Initially, fat accumulates in the liver increasing insulin resistance. This is followed by hyperinsulinemia, which leads to the release of cytokines, disruption in energy homeostasis, and variations in the hepatocyte's extracellular components. Together, these factors contribute to oxidative stress and oxidation of the accumulated fatty acids [57]. In other words, MAFLD is thought to result from the accumulation of fats in hepatocytes due to disruptions in the homeostatic mechanisms that normally regulate lipid synthesis in the liver. Furthermore, studies examining the signaling pathways and genetic variants contributing to MAFLD pathophysiology have identified multiple candidate gene variants involved in DNL, mitochondrial energy utilization, lipid catabolism, and fatty acid compartmentalization [58]. To illustrate, the rise in fructose consumption is one of the common lifestyle changes that are thought to contribute to the elevated incidence of MAFLD [59, 60]. This is because fructose consumed by the organism will be processed into glucose in the intestine, while the excess amounts will be metabolized by the gut microbiota into

Table 1 Summary of the role of ACSS2 in the pathogenesis of metabolic diseases and the possible therapeutic interventions

Disease	Role of ACSS2 in Disease Pathogenesis	Pathogenic Mechanisms	Possible Therapeutic Intervention	Reference
MAFLD	Lipogenic	- Enhance production of acetyl-CoA from excess acetate for feeding the De Novo Lipogenesis pathway - Promote lipid synthesis, accumulation, and deposition - Increase liver mass and triglyceride content	Normalizing the activity of ACSS2 by using ACSS2 chemical inhibitors	[22]
	Regulatory	- Promote the transcription of lipogenic genes (CD36 and FABP1)		
Obesity	Lipogenic	- Promote lipogenesis - Increase body weight - Increase fat mass - Promote adipose tissue accumulation	The use of ACSS2 inhibitors Regulating glucose and lipid homeostasis through targeting ACSS2 regulation Targeted ACSS2 activation in adipose tissues to promote its thermogenic capacity rather than fat accumulation	[22, 74, 76]
	Regulatory	- Mutated ACSS2 (ACSS2 S263A) show decreased phosphorylation - Reduce insulin-responsive AKT phosphorylation - Promote triglyceride accumulation - Reduce insulin sensitivity		
Diabetes	Regulatory	- Promote histone benzoylation - Induce inflammation and apoptosis in pancreatic islet β cells - Impair insulin secretion - Increase ACSS2 expression levels upon the inhibition of glucagon signaling leading to increased LDL-C levels - Elevate the risk of developing cardiovascular disorders in diabetic patients	Rational inhibition of ACSS2, besides glucagon signaling inhibition, can decrease the burden of diabetes and its complications in the patients	[82]
Acute Kidney Injury (AKI)	Regulatory	- Increase expression of transcription factors: KLF5 - Increase levels of inflammasome pathway-related genes: nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3 (*NLRP3*), caspase-1 and *IL1-β* - Promote pyroptosis in renal tubular cells	Regulation of inflammasome activation through the regulation of ACSS2 activity	[87]
Kidney Fibrosis	Regulatory	- Express key DNL genes such as *FASN* - Activate mROS and NLRP3 inflammasome - ACSS2-mediated DNL intensifies NLRP3 inflammasome pathway-dependent pyroptosis in tubule cells - Promotes IL-1β production and macrophage activation.	Pharmaceutical targeting of ACSS2 or De Novo Lipogenesis for treating kidney fibrosis	[85, 88]
Diabetic Nephropathy (DN)	Regulatory	- Enhance the acetylation levels of histone H3K9 - Activate Raptor expression and mTORC1 pathway - Inhibit autophagy and contributes to the progression of DNL	Pharmaceutical inhibition of ACSS2 to promote autophagy	[90]
Inflammation	Regulatory	- Regulation of proinflammatory cytokines expression through the acetylation of histones of pro-inflammatory cytokine genes. - Regulation of immune cells through enhancing fatty acid oxidation (FAO) for inducing Treg and B10 cell differentiation		

acetate. This acetate will be transferred via the hepatic portal vein to the liver where it will be metabolized through the DNL pathway -into fat deposits in the liver [59, 61]. Since the DNL requires the conversion of acetate into acetyl-CoA, it was commonly thought that ACLY is the primary contributor to the acetyl-CoA pool for fructose-induced DNL. However, the deletion of ACLY failed to suppress fructose-induced DNL suggesting that this process may be activated in an ACLY-independent manner [59]. Interestingly, ACSS2 appears to be a component of the hepatic response to fructose consumption, as its expression is activated by the carbohydrate response element binding protein (ChREBP) and upregulated following fructose feeding, notably in ACLY-depleted mice, suggesting that ACSS2 is providing the acetyl-CoA pool needed for DNL in the liver. In addition, tracing ACSS2 genomic locus showed an increase in histone H3K27 acetylation after fructose consumption, further showing that ACSS2 expression is activated. Thus, ACSS2 plays a role in DNL upon excess fructose consumption, contributing to the accumulation of triglyceride in the liver [59]. This suggests that ACSS2 can be considered for further examination when studying MAFLD as it is participating in DNL, a major MAFLD pathophysiology pathway.

Similarly, Yenilmez et al. studied the relative contribution of ACLY and ACSS2 in hepatic steatosis. Hepatocytes-selective depletion of either ACLY, ACSS2, or both in chow-fed and HFD-fed mice revealed that obese mice require the presence of both enzymes to maintain normal acetyl-CoA levels. Then, upon ACLY deletion,

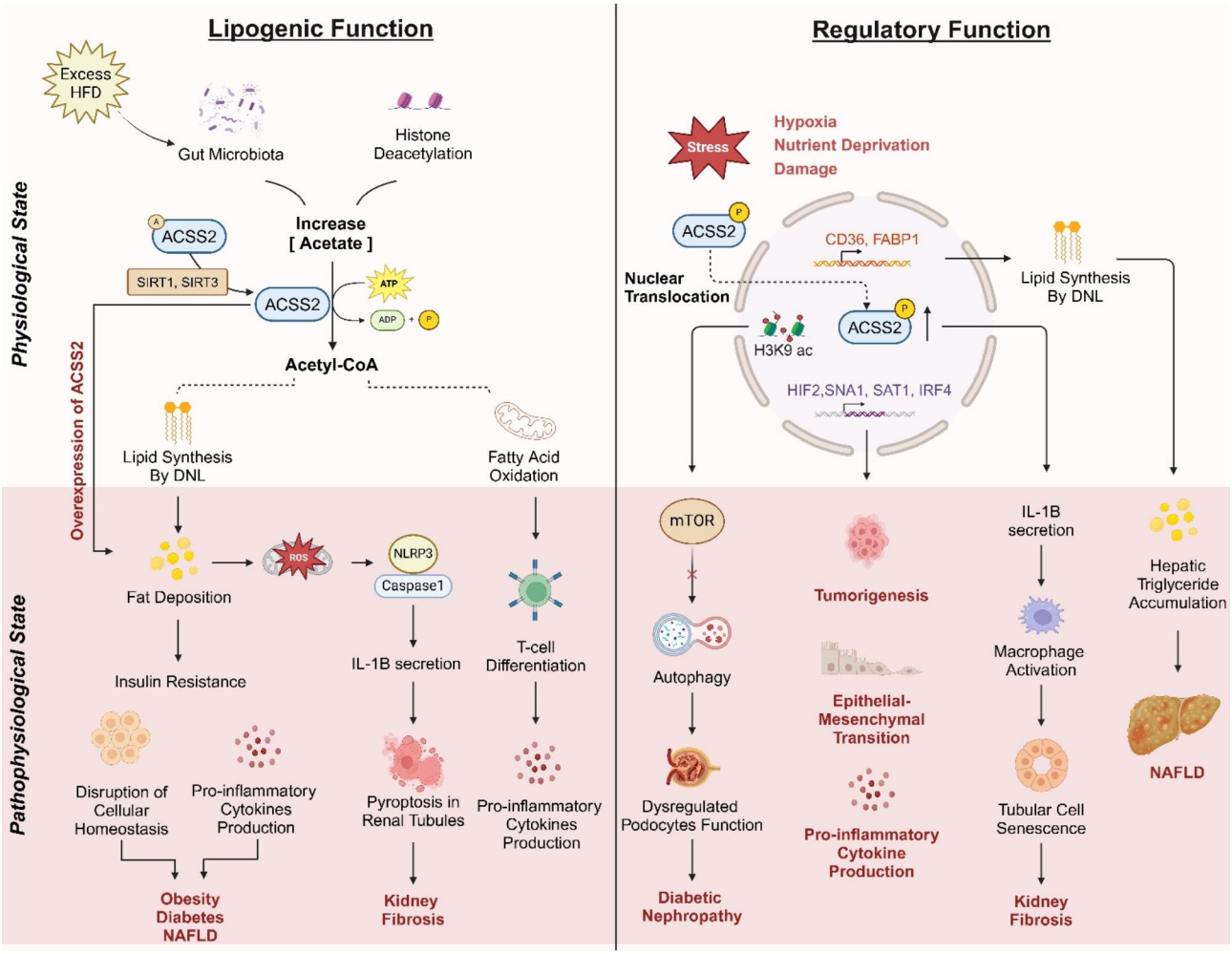

Fig. 1 The Dual Role of ACSS2 and its Correlation to Metabolic Diseases: ACSS2, with its nucleo-cytosolic nature, plays a significant role in the development of metabolic diseases by participating in various lipogenic or regulatory pathways: **(1) ACSS2 Cytosolic Lipogenic Role**: Upon the consumption of a high-fat diet, excess fats are metabolized by colonic microbiota into acetate. ACSS2, in its deacetylated active form, converts this exogenous acetate or that from endogenous histone deacetylation reactions into acetyl-CoA. This acetyl-CoA normally functions in the fatty acid oxidation in the mitochondria or in lipid synthesis by feeding the de novo lipogenesis pathway (DNL). Overexpression of ACSS2, associated with the manifestations of metabolic diseases, promotes increased lipid synthesis via DNL and fat deposition. This leads to the development of insulin resistance, disrupting cellular homeostasis and triggering the release of proinflammatory cytokines—features linked to obesity, diabetes, and MAFLD. Additionally, lipid accumulation elevates reactive oxygen species (ROS) and NLRP3-inflammasome-mediated kidney fibrosis. Enhanced fatty acid oxidation (FAO) also supports T-cell differentiation, contributing to heightened immune responses. **(2) ACSS2 Nuclear Regulatory Role**: Under stress conditions, such as hypoxia, nutrient deprivation, or cellular damage, ACSS2 phosphorylation exposes its nuclear localization signal, facilitating its translocation into the nucleus. In the nucleus, ACSS2 plays regulatory roles by promoting histone acetylation and activating the transcription of genes that support cell survival under stress conditions. ACSS2 activates genes involved in lipid synthesis and metabolism, further enhancing DNL and increasing fat accumulation, which is associated with NAFLD. It also activates genes that promote tumorigenesis, epithelial-to-mesenchymal transition (EMT), and proinflammatory cytokine production. Furthermore, ACSS2's role in histone acetylation activates the mTOR pathway, inhibiting autophagy and disrupting normal cellular functions, leading to complications such as kidney injury in diabetic conditions, also known as diabetic nephropathy. ACSS2 overexpression also promotes kidney fibrosis through IL1b secretion and macrophage activation. This dual role of ACSS2, both in the cytosol and the nucleus, underscores its significance in metabolic diseases and highlights potential therapeutic targets for intervention. (Figure designed using BioRender with a publication license.)

the enzymes involved in DNL are upregulated and this is associated with a compensatory upregulation of ACSS2 and reduction in acetate levels, suggesting that ACSS2 is converting this acetate into acetyl-CoA that feeds the DNL pathway [62]. These findings are supported by the results of another study examining the role of ACSS2 in MAFLD which showed that the expression of ACSS2 in the hepatocytes of mice fed HFD specifically increases the risk of developing hepatic steatosis. Although no significant changes were observed in $ACSS2^{+/+}$ and $ACSS2^{-/-}$ mice fed a chow diet, exposing these mice to a HFD revealed a notable difference. While $ACSS2^{+/+}$ and $ACSS2^{-/-}$ mice had comparable liver mass, morphology, and triglyceride content on a chow diet, these parameters

were significantly different under HFD conditions. The knockout of the gene in ACSS2$^{-/-}$ mice led to decreased liver mass and triglyceride accumulation, which consequently reduced the risk of developing hepatic steatosis. Specifically, there was a decrease in the transcription regulators of lipid metabolism genes and fatty acid transporters such as CD36 and FABP1 in *ACSS2*$^{-/-}$ mice. Consequently, lipid metabolism and circulation in the liver were reduced, which correlated with decreased fat accumulation and reduced risk of developing hepatic steatosis [22].

Although there are currently no approved drugs for MAFLD, and considering the adverse side effects associated with currently used drugs, there is a pressing need to develop safe and efficient treatments [63, 64]. Such approaches might aim to reverse the factors contributing to the pathogenesis of MAFLD by inhibiting the expression of genes responsible for lipid deposition in the liver. Gypenosides (GP), extracted from the plant *Gynostemm Pentaphyllum*, can be considered an example of a compound that contributes to lipid metabolism regulation, anti-cancer, anti-inflammatory, and anti-MAFLD mechanisms [65]. To investigate the mode of action of GP, Zhou et al. conducted experiments on control mice and mice fed with HFD, treated or not with GP. It was observed that GP reduces lipid levels and fat accumulation, thereby alleviating hepatic steatosis. This effect is achieved by downregulating the expression of multiple genes involved in fatty acid synthesis, including ACLY and ACSS2, whose expression decreased by approximately 64 and 67 folds, respectively. These findings were further confirmed by proteomics data, which also showed a reduced expression of ACLY and ACSS2 proteins in GP-treated mice compared to untreated mice on the HFD. This suggests that GP exerts its anti MAFLD role by inhibiting fat accumulation and enhancing its metabolism through the regulation of multiple genes involved in these pathways [65].

Collectively, these studies signify that activation of ACSS2 plays a crucial role in excessive fat accumulation by modulating the activity of genes responsible for lipid synthesis and the pathophysiology of hepatic steatosis. This suggests that targeting ACSS2 with the aim of normalizing its gene activity could represent a promising therapeutic strategy for the regulation of the corresponding lipogenic gene activation and the treatment of MAFLD.

ACSS2 and obesity

Obesity, as defined by the World Health Organization (WHO), is a chronic disease characterized by excessive fat deposits. This condition can lead to complications including type 2 diabetes, cardiovascular disorders, bone health issues, and an increased risk of cancer. Obesity is defined in adults as having a body mass index (BMI) of 30 kg/m^2 or higher [66]. Studying the pathophysiology of obesity has shown that it is a multifactorial disorder due to more than just lifestyle factors affecting food content and fat accumulation. It is also correlated with family history and genetic predisposition, the role of gut microbiota, as well as epigenic modulations involved in the regulation of metabolism. These factors collectively impact the risk of developing obesity and its associated complications [67–71].

Obesity is characterized by increased lipogenesis, which is a key contributor to its development and associated disorders. ACSS2 plays a pivotal role within these mechanisms. Research has highlighted that the gut microbiota may influence fat deposition, likely through regulating microRNAs (miRNAs) that impact lipid synthesis pathways [72]. Specifically, a study examining fat deposition in chickens, comparing the hepatic gene expression of obese chickens to those fed a normal-diet, revealed that obesity is associated with a reduction of butyric acid – a key link between gut microbiota and the liver- and a downregulation of hepatic miR-204 expression. This leads to the upregulation of ACSS2, a target of miR-204, and increased lipogenesis. These findings suggest that under HFD, butyric acid/miR-204/ACSS2 axis plays a significant role in fat deposition, where the upregulation of ACSS2 promoted lipogenesis confirming the involvement of ACSS2 in the development of obesity [72]. These results are in agreement with the findings of a similar study that examined gut microbiota – liver interaction and its role in lipogenesis. Obese chickens on HFD exhibit an upregulation of ACSS2, PCSK9, and CYP2C18 genes, leading to enhanced lipogenesis in the liver [73]. Complementary research on mice model supports these findings, as ACSS2-null mice exposed to HFD had lower body weight, reduced fat mass, and lower adipose tissue accumulation compared to *ACSS2*$^{+/+}$ mice, demonstrating that ACSS2 contributes to obesity onset [22]. This suggests that ACSS2 inhibition could offer protective effects against HFD-induced obesity.

In obesity, ACSS2 is also involved in lipogenic enzyme regulation through phosphorylation. Shaik et al. identified that AKT activity, a critical regulator of lipid metabolism, glucose uptake, and insulin signaling, is impaired in mice fed with HFD, correlating with dephosphorylation of ACSS2 and other lipogenic enzymes. Dephosphorylation at the S263 residue on ACSS2, observed in obesity models, was confirmed in vitro in adipocyte cells, where its mutation led to triglyceride accumulation and reduced insulin sensitivity [74]. These findings underscore the impact of ACSS2 in lipogenesis, highlighting its role in obesity-associated metabolic dysfunctions. In addition to its role in lipogenesis, ACSS2 was also found to be involved in the progression of obesity-induced disorders such as obesity-induced myeloma. The increase in

the mass of adipocytes is associated with tumor growth as tumorigenesis is supported in adipocyte-rich tumor microenvironment. In order to understand the relationship between adipocytes mass and tumorigenesis, analysis of adipocytes isolated from obese patients identified elevated expression of ACSS2, which is crucial under conditions of hypoxia and stress, key features associated with tumors. ACSS2 interacts with oncoproteins such as interferon regulatory factor 4 (IRF4), which plays a role in immune cell development and response. This interaction allows IRF4's acetylation and stability, enabling it to escape the lysosome-mediated degradation process. As a result, IRF4 protein levels increase, promoting the transcription of genes that support myeloma growth and survival. These findings were further confirmed by testing the effect of ACSS2 inhibition in both in vitro myeloma cell lines and in vivo obesity-induced mouse models. ACSS2 inhibitor significantly reduced IRF4 protein levels in myeloma cells inducing apoptosis, and impairing myeloma growth [36]. These findings support the role of ACSS2 in facilitating tumor progression within an obesity context.

With the complex interplay between different factors leading to obesity, effective treatment options remain limited. Bariatric surgery is often regarded as the most effective method for treating morbidly obese patients [75]. However, the success rate in terms of weight loss and the reduction of obesity-related complications vary among patients. Research revealed that the procedure outcome is highly dependent on the metabolic state of the patients' adipose tissue before the surgery. For instance, recent studies suggest that ACSS2 expression levels within adipose tissue may impact treatment outcomes. Morbidly obese patients with initially lower ACSS2 expression experienced a greater reduction in body weight. An explanation of this might be directly related to the role of ACSS2 in DNL and lipid synthesis. Lower ACSS2 expression and activity results in reduced lipid synthesis, which consequently leads to a higher percentage of weight loss upon treatment [75]. This insight positions ACSS2 as not only a target in obesity prevention but also a potential marker for predicting responsiveness to bariatric interventions.

The study by Chen et al. further elucidates the dual role of ACSS2 in obesity, particularly in adipose tissue thermogenesis and beiging. While previous studies, as discussed, have identified ACSS2's involvement in lipogenesis and fat accumulation under HFD conditions, the new findings highlight ACSS2's role in promoting energy expenditure through thermogenesis in brown adipose tissue (BAT) and the induction of beiging in white adipose tissue (WAT). ACSS2 was found to bind PPARγ in a ligand-dependent manner, recruiting SIRT1 to deacetylate PPARγ, which maintains optimal transcriptional activity necessary for adipose tissue plasticity. Moreover, in cold-stimulated conditions, ACSS2 knockout mice showed lower body temperatures, reduced oxygen consumption, and diminished heat production compared to wild-type mice. Notably, D-mannose, a natural sugar and rapid inducer of ACSS2, was shown to stimulate this thermogenic pathway in adipose tissues, suggesting a potential therapeutic approach that leverages ACSS2's role in energy expenditure rather than fat accumulation [76]. These findings introduce a novel perspective on ACSS2's function, where targeted activation in adipose tissues could counter obesity by enhancing thermogenic capacity, contrasting with its previously recognized role in promoting lipogenesis and fat deposition in liver tissues. In addition, revealing the role of ACSS2 in the thermogenic ability adds to the growing literature new functions to the enzyme that can be used for its therapeutic modulation, especially that earlier studies initially associated ACSS1 with the thermogenesis processes without highlighting the possible contribution of ACSS2 too [77]. Together, this research suggests that selective tissue modulation of ACSS2 may open new avenues for obesity treatment by balancing lipogenesis with mechanisms that increase metabolic rate.

ACSS2 and diabetes

Diabetes mellitus (DM), commonly known as diabetes, is a chronic metabolic disease mainly characterized by high levels of glucose in the blood (hyperglycemia). The disease can manifest as type one diabetes mellitus (T1DM), resulting from the pancreas producing insufficient amounts of insulin, an essential hormone needed to convert glucose into energy, or type 2 diabetes mellitus (T2DM) which is due to a combination of insulin resistance and inadequate insulin secretion. Gestational diabetes mellitus (GDM) is considered a third type of diabetes, known as a form of glucose intolerance, that occurs during pregnancy, with most cases resolving after delivery [78]. Clinical symptoms of diabetes primarily reflect hyperglycemia and include polyuria, polydipsia, polyphagia, weight loss, and blurred vision [78].

Histone post-translational modifications (HPTM) are among the prominent epigenetic regulations linked to the development of diseases such as diabetes. One such HPTM is benzoylation, induced by sodium benzoate, which has been found to be involved in inducing inflammation and apoptosis in pancreatic islet β cells. Consequently, this leads to insulin secretion damage associated with diabetes. For this modification to occur, benzoylate must be converted to benzoyl-CoA. This was confirmed by measuring the benzoyl-CoA concentrations in the serum of healthy and diabetic patients, where diabetic patients had significantly higher levels of benzoyl-CoA. ACSS2, being an enzyme that allows the conversion of

short chain fatty acids to their active CoA ligated molecules, is suggested to have a role in this mechanism. To prove the role of ACSS2 in the process, β-TC-6 cells were stimulated with sodium benzoylate, treated or not with ACSS2 inhibitor. Enzymatic inhibition led to reduced benzoyl-CoA levels, marked by a reduction in inflammatory and apoptotic markers, indicating a reversal of the damage affecting insulin secretion, and proving the role of ACSS2 in the alterations leading to diabetes [79, 80]. This shows that ACSS2 might have a role in initiating the pathophysiological pathways, such as impaired insulin secretion, and other complications associated with diabetes. Interestingly, another study revealed that ACSS2 is recognized as a key factor in the metabolic processes associated with diabetes. For instance, analyzing the differential gene expression in the tissues of pregnant mice fed with HFD suggested that multiple genes, including ACSS2, might be involved in the pathogenesis of gestational diabetes [81].

Interestingly, diabetes treatments have been found to affect the expression levels of ACSS2. For example, antagonizing the glucagon receptor (GCGR) is one of the treatment strategies for diabetes, given that hepatic overproduction of glucose and subsequent hyperglycemia are associated with the disease. Inhibiting GCGR may help lower plasma glucose levels. This can occur through the inhibition of glucagon signaling, mediated by GCGR knockdown in mouse models. While hepatic GCGR knockdown resulted in reduced plasma glucose levels, which is beneficial for treating diabetes, LDL-C levels increased. This is considered an unfavorable side effect, contributing to an elevated risk of developing cardiovascular disorders in diabetic patients. Further analysis revealed that this increase in LDL-C levels was correlated with elevated levels of several hepatic lipogenic genes, including ACSS2 [82]. This suggests that a more rational approach, involving the inhibition of ACSS2 and similar lipogenic genes in addition to glucagon signaling inhibition, could lead to a better overall impact by reducing the burden of diabetes and its associated complications in patients.

Glucose intolerance refers to a condition where blood glucose levels are higher than normal, but not high enough to be classified as diabetes. It can serve as an early identification factor to prevent the progression to T2DM [83]. Studies on ApoE3Leiden transgenic mice (ApoE3L), which have a humanized lipid metabolism process and are fed with HFD to create a glucose intolerance model, identified some prognostic and diagnostic markers of glucose intolerance. A significant negative correlation between ACSS2 gene expression in white blood cells and the degree of glucose intolerance was established. Specifically, a low ACSS2 expression level in white blood cells indicates a high level of glucose intolerance. This negative correlation was also apparent when tracking the ACSS2 expression in the white blood cells over different timepoints. Monitoring of ACSS2 expression over time allowed tracking the degree of glucose intolerance as the disease progresses. These ACSS2 expression levels were also correlated with the concentrations of citric acid cycle intermediates in the liver, affecting energy production cycles that are necessary under ketogenic conditions such as diabetes. This highlights the significance of ACSS2 in energy metabolism and insulin activity, suggesting that low ACSS2 levels serve as a diagnostic marker for glucose intolerance [83]. This proposes ACSS2, having a role whether in effecting energy production pathways or as a post-translational regulator, is a potential target for further study to understand its role in the mechanisms underlying glucose intolerance, diabetes, and related disorders and develop efficient treatments.

ACSS2 and renal diseases

Kidneys are metabolically active organs essential for maintaining electrolyte and fluid homeostasis, and responsible for excreting waste products and toxins from the body following each round of a normal metabolic pathway [84]. Dysregulation of the kidney's metabolic function due to kidney damage and alteration in blood filtration processes is associated with the development of renal diseases, which are serious global health issues. ACSS2, being a crucial regulator of several metabolic pathways, can contribute to the emergence of renal diseases.

Acute kidney injury (AKI) is a serious complication characterized by a rapid decline in renal function and death of renal tubular epithelial cells. The primary pathological features of AKI include pyroptosis, a form of proinflammatory programmed cell death, and interstitial inflammation [79]. Recent studies demonstrated a correlation between ACSS2 and AKI, where ACSS2 appeared to enhance pyroptosis in renal tubular cells [85, 86]. To further examine the role of ACSS2 in the inflammatory responses associated with AKI, a study showed that ACSS2 expression is significantly increased in the renal epithelial cells in mice with LPS-induced AKI. However, AKI is attenuated upon the inhibition of ACSS2. In addition, treatment of HK-2 cells with LPS resulted in increased expression of the Krüppel Like Factor 5 (KLF5), a transcription factor involved in various cellular processes including cell proliferation, differentiation, and inflammation, as well as increased levels of inflammasome pathway-related genes including nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3 (NLRP3), caspase-1 and IL1-β which are normally activated by NF-κB. Conversely, ACSS2 deletion reduced these LPS-induced levels. Thus, ACSS2 activates the KLF5/NF-κB mediated caspase-1

inflammatory pathway, which in turn promotes the activation of the NLRP3 inflammasome and enhances pyroptosis in renal tubular epithelial cells [87]. Although the exact molecular mechanisms by which ACSS2 induces pyroptosis in renal tubular cells remain elusive, existing evidence suggests that ACSS2 plays a significant role in promoting pyroptosis in renal disorders. This observation highlights ACSS2 as a potential and promising therapeutic target.

Other than triggering pyroptosis, ACSS2 was identified as a kidney disease risk gene that can also promote kidney fibrosis in kidney diseases. Interestingly, in adenine-induced kidney disease models, *ACSS2*$^{-/-}$ mice showed less renal tubular injury and fibrosis compared to wild type mice. This was marked by measuring the indicators of kidney dysfunction such as serum creatinine (sCr) and blood urea nitrogen (BUN), which were higher in wild type mice. Genetic deletion of ACSS2 in mouse kidney tubule cells exhibited reduced expression of key DNL genes such as FASN compared to WT cells, showing that ACSS2 regulates DNL of these cells. Moreover, lower activity of mROS and NLRP3 inflammasome was reported in kidney tubule cells subjected to *ACSS2* knockdown compared to wild type cells treated with TGF-β1 to induce fatty acid synthesis. This indicates that ACSS2-mediated DNL leads to elevated ROS levels and intensifies NLRP3 inflammasome pathway-dependent pyroptosis in tubule cells, highlighting the importance of ACSS2 in the development of kidney fibrosis [85].

Although mixed findings were found before regarding the effect of ACSS2 on crotonate as a substrate [16, 17, 19], ACSS2 dependent crotonylation was observed in renal cells, and further linked to pathogenesis processes. Upon studying the effect of histone crotonylation in kidney fibrosis, researchers found that ACSS2 overexpression in both mouse renal tubular epithelial cells, and human embryonic kidney cells is correlated with increased histone 3 lysine 9 crotonylation (H3K9cr) which in turn promotes IL-1β production and influences macrophage activation thereby promoting kidney fibrosis. This was further demonstrated through genetic deletion of ACSS2 which suppressed H3K9cr in *ACSS2*$^{-/-}$ mice and alleviated kidney fibrosis [88]. Overall, this highlights the proinflammatory action of ACSS2 in renal diseases, and the importance of targeting ACSS2 to protect against kidney fibrosis.

Upon examining diabetic nephropathy (DN), a subtype of renal diseases, and a further renal complication associated with diabetic patients, ACSS2 expression was shown to be upregulated in the podocytes of DN patients and diabetic mouse models [89]. The overexpression of ACSS2 in high glucose-treated podocytes increased the acetylation levels of histone H3K9, which activated Raptor expression and consequently led to the activation of the mammalian target of rapamycin complex 1 (mTORC1) pathway. This inhibits autophagy and contributes to the progression of DN. Conversely, the knockdown of ACSS2 in streptozotocin-induced diabetic mice reduced kidney injury and instead enhanced podocyte autophagy by increasing the LC3II/I ratio, a key autophagy marker, while decreasing p62 level in podocytes. This suggests that ACSS2 inhibition protects against kidney injury in DN patients [90]. Additionally, ACSS2 inhibition ameliorates high-glucose-induced decrease in nephrin expression, suppresses α–smooth muscle actin (α-SMA) expression in podocytes, and alleviates the inflammatory cytokine expressions of TNF-α, IL-6, and monocyte chemoattractant protein-1 (MCP-1) in high-glucose-treated podocytes [90]. This shows that ACSS2 upregulation promotes podocyte injury, suggesting that ACSS2 could be a potential therapeutic target in DN patients. Overall, ACSS2 appears to play a role in renal disorders by influencing key metabolic and epigenetic processes where it has been linked to pyroptotic cell death and the progression of kidney fibrosis, both of which contribute to kidney injuries. These findings collectively highlight ACSS2 as a potential therapeutic target for mitigating inflammation, reducing kidney fibrosis, and preserving kidney functions in renal disorders.

ACSS2: a metabolic regulator in inflammatory and immune responses

Inflammation is a natural defense mechanism initiated by the host's immune system to overcome any pathological or harmful invasion. However, chronic untreated inflammation may lead to the emergence of new comorbidities. Inflammation and the tissue microenvironment significantly contribute to the development of metabolic syndrome, encompassing conditions such as obesity, insulin resistance, non-alcoholic liver disease, and diabetes [91–93]. For example, multiple studies examined the relationship between obesity, a major risk factor for multiple other metabolic disorders, and chronic inflammation [94]. It was shown that obesity leads to the infiltration of macrophages in mice and human obesity cases, with elevated secretion of pro-inflammatory cytokines that eventually lead to insulin resistance and its associated complications [94–96]. Thus, various components of inflammation, including immune cells and mediators of the innate immune system, are key contributors to the development of metabolic disorders. A meta-analysis conducted to characterize blood samples from type 2 diabetic patients detected an elevated expression of inflammatory cytokines such as IL-1β, IL-16, IL-18, C-reactive protein (CRP) and TNF-α [97]. Similarly, higher levels of TNF-α are reported in the serum of obese diabatic patients compared to both non-obese diabetic and obese non-diabatic patients [98]. Recently, a study revealed

that the irregular production of adipocytokines and disturbances in lipid metabolism could collectively trigger inflammatory signaling pathways, thus playing a role in the ongoing inflammation characteristic of the progression of MAFLD. Serum analysis revealed a substantial increase in the levels of several inflammatory cytokines and chemokines (IL-1, IL-1β, chemokine ligands: CCL2, CCL3, CCL4, CCL5) promoting the progression of MAFLD [99]. Hence, examining the contributors to the development of inflammation associated with metabolic disorders might provide a better understanding of the pathogenesis of these diseases.

Although ACSS2 is considered a major metabolic regulator, recent evidence suggests that it is also associated with several inflammatory responses. For instance, a study revealed that a targeted deficiency in SREBPs of LPS-stimulated mice macrophages, specifically SREBP-1a, caused a reduction in pro-inflammatory cytokines mainly IL-1β and IL-12 and caused an impairment in the inflammasome activity compared to that of WT mice macrophages. SREBP-1a, a transcription factor for ACSS2, acts as a link between lipid metabolism and the immune response by targeting genes such as NLRP1a, which is involved in the activation of inflammasomes and inflammatory cytokine production [100]. Interestingly, ACSS2 was found to be upregulated in the absence of ACLY, whose deficiency resulted in the upregulation of inflammatory genes; this suggests an indirect link between ACSS2 and inflammatory gene expression in adipocytes [101]. Similarly, researchers have proposed that the elevated inflammatory response observed in ACLY-deficient macrophages could potentially be attributed to the influence of an increased activation in ACSS2 [102].

Other reports showed that the production of metabolically available acetyl-CoA from acetate, facilitated by ACSS2, is essential for the acetylation of histones of pro-inflammatory cytokine genes. This process leads to the escalation of the inflammatory response in macrophages exposed to ethanol [103]. ACSS2 was also found to regulate cytokine production by serving as a substrate for the biosynthesis of platelet activating factor (PAF), a lipid mediator involved in various physiological processes with an autocrine function in the production of cytokines [104].

Besides its role in cytokine production, ACSS2 is also associated with the regulation of several immune responses, through the regulation of different immune cells. As part of the immune system, regulatory T (Treg) cells are specialized subsets of the CD4 + T cells that serve as immune suppressors [105]. However, some studies showed that Treg could also induce inflammation through producing pro-inflammatory cytokines such as IL-17 under certain inflammatory conditions [106, 107]. ACSS2 was shown to enhance fatty acid oxidation (FAO) inducing Treg differentiation. Moreover, it converts butyrate to butyryl-CoA (BCoA), feeding the beta oxidation pathway and further supporting iTreg differentiation [108]. Similar studies also revealed the role of ACSS2 in supporting the differentiation of other immune cells such as the B10 cell differentiation [109]. B10 cells, which are also known as the IL-10–producing regulatory B cells, have important anti-inflammatory roles in which they decrease the severity of autoimmune diseases such as encephalitis and arthritis [110, 111]. A study on the acetate mediated B10 cell differentiation proposed that ACSS2 is an important enzyme involved in the process. It converts acetate into acetyl-CoA associated with the increased protein-lysine acetylation and thus participates in the differentiation process. This was clearly demonstrated where upon the blockage of mitochondrial metabolism and the inhibition of ACLY activity, no significant effect on the IL-10 secretion or the B10 cell differentiation was reported, indicating that such processes are occurring due to pathways other than the mitochondrial TCA cycle. On the contrary, inhibiting ACSS2 decreased the acetate-induced B10 cell production in both in vitro and in vivo conditions, further highlighting the importance of ACSS2 in the immune cell production and inflammatory response regulation [109]. Hence, such studies collectively suggest that ACSS2, through regulating the immune cells differentiation, might be also involved in the regulation of inflammatory responses and its dysregulation might be one of the contributors to autoimmune diseases.

ACSS2 has been correlated with several autoimmune diseases such as psoriasis. Psoriasis is an autoinflammatory skin disease influenced by genetic factors and mutations that cause the appearance of patches of thick skin known as plaques. Psoriasis is associated with several metabolic diseases where most psoriasis patients exhibited a higher risk of obesity, type 2 diabetes, hepatic steatosis, and liver fibrosis [112–114]. In the progression of psoriasis, the interleukin IL-23/IL-17 pathway stands out within the primary cytokine cascade, enhancing the progression of the disease [115]. Psoriasis has also been linked to ACSS2 expression, where it is among the top 50 differentially expressed genes, typically downregulated in the peripheral edge of lesional skin in psoriasis patients [105]. In an attempt to test the effect of silymarin (SM), a plant extract having antiproliferative, pro-differentiation, and anti-inflammatory effects on epidermal cells, it was deduced that SM also regulates the expression of lipogenic genes that are commonly dysregulated in skin diseases such as psoriasis. TGF- β1 induced psoriasis in HaCaT cells showed a significant increase in ACSS2 upon SM treatment compared to cells treated with TGF-β1 only. The increase in lipogenic genes such as ACSS2

Table 2 Summary of the drugs that might impact the expression/activity of ACSS2

Molecule/Drug	Indication	Impact on ACSS2 expression	Mechanism of Action
Gypenosides	- Lipid metabolism regulation - Anti-cancer - Anti-inflammatory - Anti-MAFLD	Downregulation	Inhibiting fat accumulation and enhancing its metabolism through the regulation of multiple lipogenic genes
Silymarin	- Antiproliferative, pro-differentiation, and anti-inflammatory effects on epidermal cells - Treatment of skin diseases such as psoriasis	Upregulation	Stimulating the expression of lipid synthesis genes to improve the skin barrier function
IB20 antibody	Treatment of coronary heart disease	Downregulation	Reducing the expression of SREBP-regulated genes to decrease fatty acid synthesis
Fuzheng-Huayu formula (FZHY)	Treatment of liver fibrosis	Downregulation	Regulating lipogenesis genes to modulate glycolysis/gluconeogenesis, the citrate cycle, galactose metabolism, tryptophan metabolism, and the urea cycle
Rapamycin	Treatment of renal and metastatic breast cancers	Direct binding and activation	Suppressing breast cancer progression through affecting cancer cells proliferation, invasion, and migration abilities
MTB-9655	Treatment of solid tumors	Direct inhibition	Inhibiting ACSS2 activity through direct binding

following SM treatment indicates that SM exerts its anti-psoriasis effect through stimulating the expression of lipid synthesis genes in psoriasis induced models, suggesting that SM is improving the skin barrier function [116]. Given that the molecular mechanisms leading to decreased lipid synthesis gene expression in psoriasis are still not clearly known, investigating the effect of lipogenic genes in the development of the disease is of great importance. With the current understanding, it is suggested that ACSS2's dysregulation and particularly due to its role as a lipogenic enzyme, might have an impact on the pathways related to the psoriasis progression and hence it is contributing to the pathophysiology of the disease. This might be explained by the differential expression of ACSS2 in the psoriasis models compared to the control, and the reversal of psoriasis complications upon its upregulation following treatment. Knowing that the disease is characterized by dysregulated lipogenic and inflammatory responses - both of which were previously correlated to ACSS2- more research must be conducted to reveal the possible contributions of ACSS2 in the different pathological pathways leading to psoriasis development.

The present literature highlighted the role of ACSS2 in the different aspects of immunity whether cytokine production, immune cells regulation, or autoimmune diseases manifestations. However, the limited amount of research in this area specifically makes it challenging to identify the exact role of ACSS2 in inflammatory diseases. Further research must be conducted in order to better understand the pro or anti-inflammatory effects of ACSS2's activity, toward considering it as an important therapeutic target for regulating inflammatory responses and their related complications.

Therapeutic potential of targeting ACSS2 in disease management

Consistent with its role in several pathways and given that its dysregulation induces the development of multiple disorders, targeting ACSS2 might be a promising therapeutic strategy for treating various diseases, including metabolic disorders (Table 2). For instance, given that ACSS2 upregulation leads to obesity and hepatic steatosis, developing an inhibitor for the ACSS2 enzyme might be an efficient treatment method for these diseases [22, 36]. Moreover, multiple studies suggested that targeting ACSS2 might be a potential therapeutic strategy for kidney-associated disorders [85, 87].

Some studies show that ACSS2 is considered a target in the treatment of other diseases. For example, proprotein convertase subtilisin/kexin type 9 (PCSK9) is a potential target for treating coronary heart disease due to its role in affecting plasma lipoprotein cholesterol levels. Such a treatment option might involve IB20 antibody, which binds to PCSK9 and antagonizes its function. Upon testing the antibody-bound effect on human hepatocytes, results revealed that IB20 antibody protects against the PCSK9 effect by reducing the expression of SREBP-regulated genes, which are commonly known for their role in fatty acid synthesis, and ACSS2 is among these genes [117]. Similarly, the Fuzheng-Huayu formula (FZHY) is used to treat liver fibrosis by regulating the expression of multiple metabolic enzymes involved in the metabolic alterations associated with liver fibrosis. Upon the administration of FZHY to rats, transcriptomic analysis identified its effect on the expression levels of metabolic enzymes, where some were upregulated, while others, including ACSS2, were downregulated compared to untreated rat models. By affecting the expression of these genes, FZHY modulates glycolysis/gluconeogenesis, the citrate cycle, galactose metabolism, tryptophan

metabolism and the urea cycle, which collectively contribute to liver fibrosis [118].

Moreover, when observing the effect of rapamycin – an FDA approved drug to treat renal and metastatic breast cancers - on cadmium-induced breast cancer progression, it was shown to inhibit cancer by directly targeting and activating ACSS2. This was proven by experiments that revealed how cadmium induction led to the suppression of ACSS2 and enhanced the proliferation and migration ability of cancer cells; upon treating with rapamycin, ACSS2 is overexpressed suppressing breast cancer progression [119]. Besides, phase I in-human clinical trials are currently being performed to test the effect of MTB-9655, a potent ACSS2 oral inhibitor developed by MetaboMed in 2021. It is described as a small molecule inhibitor of ACSS2 for use in advanced solid cancers such as colorectal, breast and lung cancers - where ACSS2 is commonly overexpressed - especially for patients with tumors that resisted the standard treatment options. After predicting its tolerance and safety profile in the preclinical studies on rodents and non-human primates, the drug is planned to be administered to around 30 solid-tumor patients once per day, over 21-day cycles, assessing drug escalation and working on dose expansion. The latest update revealed that, up until now, the oral inhibitor was tested on 10 patients and was shown to be absorbed rapidly after administration; yet dose escalation study is continuing [120, 121].

With the existing research on the possibility of using oral inhibitors to treat ACSS2-related tumors, and with the presence of promising results so far, it is suggested that ACSS2-targeting drugs can be also used to treat other diseases, particularly metabolic disorders. The current knowledge suggests that ACSS2 can be involved in the manifestations associated with the pathophysiology of metabolic disorders, and its expression levels might greatly impact the metabolic pathways and thus the disease conditions and the patients' responsiveness to treatments. Hence, with more research on the role of ACSS2 in the development of such diseases, it will become possible to target ACSS2, as with the oral inhibitor, as a new and promising therapeutic strategy for the treatment of metabolic disorders.

Review's strengths and limitations

The review provides a thorough analysis of various studies examining the role of ACSS2 in metabolic disorders, offering a well-rounded summary of its contributions to these diseases. By including studies that highlight ACSS2's lipogenic functions alongside those emphasizing its regulatory roles, the review delivers a comprehensive understanding of the enzyme's diverse potential impacts. It effectively presents complementary and conflicting findings from the literature, offering insights into ACSS2's multifaceted roles and identifying gaps in knowledge that warrant further investigation.

However, the relatively limited number of studies on certain aspects of the review's topics poses challenges in fully interpreting ACSS2's true effects. The conclusions could be further refined and substantiated with additional research. For instance, a notable gap in the literature is the lack of focus on ACSS2's role in autoimmune diseases, as well as the unclear distinction between whether its upregulation is a causative factor in disease or a consequence of it. Future studies addressing these gaps would provide a more definitive understanding of ACSS2's involvement in metabolic disorders.

Conclusion

With the continuous global increase in the prevalence of metabolic disorders, these conditions are now regarded as a serious issue threatening the lives of billions of people worldwide. The current findings on ACSS2 and its functions highlight an interesting and growing area in research. Studies indicate that ACSS2 may act as both a metabolic and inflammatory regulator, playing a role in the pathogenesis and progression of several metabolic disorders, including hepatic steatosis, obesity, diabetes, and renal diseases. The enzyme's proven role as not only a lipogenic contributor but also a crucial metabolic regulator opens the chance for further investigations for targeting this enzyme in therapy. Indeed, current research has shown that ACSS2 participates in multiple pathways that promote tumorigenesis especially in a metabolically challenged microenvironment, with promising results on the use of ACSS2 inhibitors as a treatment option. The ongoing investigation of the clinical application of ACSS2 inhibitors, particularly in cancer therapies currently in development, presents opportunities to extend this approach to other diseases where ACSS2 plays a major role in the disease development and progression. The current literature on ACSS2 and metabolic disorders underscores the promising potential of ACSS2 targeted therapies to mitigate the effects of ACSS2 on these diseases, as evidenced by the reversal of disease pathogenesis following ACSS2 inhibition or knockdown. However, with relatively few studies investigating the role of ACSS2 as a potential therapeutic target in metabolic disorders as compared to cancer for example, more research is needed to better understand the mechanisms underlying the role of ACSS2 in the progression of these diseases and thus find safe treatments.

Author contributions

A.K. and R.A. wrote the main text and prepared the figure. A.K., R.A., and Q.A. revised the manuscript. J.N.I. and P.H.K. reviewed, proofread, and revised the manuscript. P.H.K. conceptualized and supervised the study.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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References

1. Chew NWS, Ng CH, Tan DJH, Kong G, Lin C, Chin YH, et al. Cell Metab. 2023;35(3):414–e4283. The global burden of metabolic disease: Data from 2000 to 2019.
2. Shimabukuro M, Zhou YT, Levi M, Unger RH. Fatty acid-induced β cell apoptosis: a link between obesity and diabetes. Proc Natl Acad Sci. 1998;95(5):2498–502.
3. Kneeman JM, Misdraji J, Corey KE. Secondary causes of nonalcoholic fatty liver disease. Ther Adv Gastroenterol. 2012;5(3):199–207.
4. Wellen KE, Hatzivassiliou G, Sachdeva UM, Bui TV, Cross JR, Thompson CB. ATP-Citrate lyase Links Cellular metabolism to histone acetylation. Science. 2009;324(5930):1076–80.
5. Zhao S, Torres A, Henry RA, Trefely S, Wallace M, Lee JV, et al. ATP-Citrate lyase controls a glucose-to-acetate metabolic switch. Cell Rep. 2016;17(4):1037–52.
6. Beigneux AP, Kosinski C, Gavino B, Horton JD, Skarnes WC, Young SG. ATP-Citrate Lyase Deficiency in the mouse. J Biol Chem. 2004;279(10):9557–64.
7. Jong-Gubbels P, Berg MA, Steensma HY, Dijken JP, Pronk JT. The Saccharomyces cerevisiae acetyl-coenzyme A synthetase encoded by the ACS1 gene, but not the ACS2-encoded enzyme, is subject to glucose catabolite inactivation. FEMS Microbiol Lett. 2006;153(1):75–81.
8. Luong A, Hannah VC, Brown MS, Goldstein JL. Molecular characterization of human Acetyl-CoA synthetase, an enzyme regulated by Sterol Regulatory Element-Binding Proteins. J Biol Chem. 2000;275(34):26458–66.
9. Watkins PA, Maiguel D, Jia Z, Pevsner J. Evidence for 26 distinct acyl-coenzyme A synthetase genes in the human genome. J Lipid Res. 2007;48(12):2736–50.
10. Fujino T, Kondo J, Ishikawa M, Morikawa K, Yamamoto TT. Acetyl-CoA synthetase 2, a mitochondrial matrix enzyme involved in the oxidation of acetate. J Biol Chem. 2001;276(14):11420–6.
11. Yoshimura Y, Araki A, Maruta H, Takahashi Y, Yamashita H. Molecular cloning of rat acss3 and characterization of mammalian propionyl-CoA synthetase in the liver mitochondrial matrix. J Biochem (Tokyo). 2016;161(3):279–89.
12. Moffett JR, Puthillathu N, Vengilote R, Jaworski DM, Namboodiri AM. Acetate revisited: a key Biomolecule at the Nexus of Metabolism, Epigenetics and Oncogenesis—Part 1: Acetyl-CoA, acetogenesis and Acyl-CoA short-chain synthetases. Front Physiol. 2020;11:580167.
13. Ariyannur PS, Moffett JR, Madhavarao CN, Arun P, Vishnu N, Jacobowitz DM, et al. Nuclear-cytoplasmic localization of acetyl coenzyme a synthetase-1 in the rat brain. J Comp Neurol. 2010;518(15):2952–77.
14. Nagati JS, Kobeissy PH, Nguyen MQ, Xu M, Garcia T, Comerford SA, et al. Mammalian acetate-dependent acetyl CoA synthetase 2 contains multiple protein destabilization and masking elements. J Biol Chem. 2021;297(3):101037.
15. ACSS2 acyl-. CoA synthetase short chain family member 2 [Homo sapiens (human)] - Gene - NCBI updated on 8-Feb-2025. https://www.ncbi.nlm.nih.gov/gene/55902#summary
16. Scaife JR, Tichivangana JZ. Short chain acyl-CoA synthetases in ovine rumen epithelium. Biochim Biophys Acta BBA - Lipids Lipid Metab. 1980;619(2):445–50.
17. Sabari BR, Tang Z, Huang H, Yong-Gonzalez V, Molina H, Kong HE, et al. Intracellular Crotonyl-CoA stimulates transcription through p300-Catalyzed histone crotonylation. Mol Cell. 2015;58(2):203–15.
18. Zhu R, Ye X, Lu X, Xiao L, Yuan M, Zhao H, et al. ACSS2 acts as a lactyl-CoA synthetase and couples KAT2A to function as a lactyltransferase for histone lactylation and tumor immune evasion. Cell Metab. 2024;37(2):361–76.e7.
19. Zeaiter N, Belot L, Cunin V, Nahed RA, Tokarska-Schlattner M, Le Gouellec A, et al. Acetyl-CoA synthetase (ACSS2) does not generate butyryl- and crotonyl-CoA. Mol Metab. 2024;81:101903.
20. Hallows WC, Lee S, Denu JM. Sirtuins deacetylate and activate mammalian acetyl-CoA synthetases. Proc Natl Acad Sci. 2006;103(27):10230–5.
21. Li X, Yu W, Qian X, Xia Y, Zheng Y, Lee JH, et al. Nucleus-translocated ACSS2 promotes gene transcription for Lysosomal Biogenesis and Autophagy. Mol Cell. 2017;66(5):684–e6979.
22. Huang Z, Zhang M, Plec AA, Estill SJ, Cai L, Repa JJ et al. ACSS2 promotes systemic fat storage and utilization through selective regulation of genes involved in lipid metabolism. Proc Natl Acad Sci. 2018;115(40). [cited 2023 Dec 22] Available from: https://doi.org/10.1073/pnas.1806635115
23. Charidemou E, Noberini R, Ghirardi C, Georgiou P, Marcou P, Theophanous A, et al. Hyperacetylated histone H4 is a source of carbon contributing to lipid synthesis. EMBO J. 2024;43(7):1187–213.
24. Mariño G, Pietrocola F, Eisenberg T, Kong Y, Malik SA, Andryushkova A, et al. Regulation of Autophagy by Cytosolic Acetyl-Coenzyme A. Mol Cell. 2014;53(5):710–25.
25. Vasudevan NP, Soni DK, Moffett JR, Krishnan JKS, Appu AP, Ghoshal S, et al. Acss2 deletion reveals functional versatility via tissue-specific roles in Transcriptional Regulation. Int J Mol Sci. 2023;24(4):3673.
26. Nagati JS, Xu M, Garcia T, Comerford SA, Hammer RE, Garcia JA. A substitution mutation in a conserved domain of mammalian acetate-dependent acetyl CoA synthetase 2 results in destabilized protein and impaired HIF-2 signaling. Imhof A, editor. PLOS ONE. 2019;14(11):e0225105.
27. Moffett JR, Puthillathu N, Vengilote R, Jaworski DM, Namboodiri AM. Acetate revisited: a key Biomolecule at the Nexus of Metabolism, Epigenetics, and oncogenesis– part 2: acetate and ACSS2 in Health and Disease. Front Physiol. 2020;11:580171.
28. Liu M, Liu N, Wang J, Fu S, Wang X, Chen D. Acetyl-CoA synthetase 2 as a therapeutic target in Tumor Metabolism. Cancers. 2022;14(12):2896.
29. Ling R, Chen G, Tang X, Liu N, Zhou Y, Chen D. Acetyl-CoA synthetase 2(ACSS2): a review with a focus on metabolism and tumor development. Discov Oncol. 2022;13(1):58.
30. Schug ZT, Peck B, Jones DT, Zhang Q, Grosskurth S, Alam IS, et al. Acetyl-CoA synthetase 2 promotes acetate utilization and maintains Cancer Cell Growth under metabolic stress. Cancer Cell. 2015;27(1):57–71.
31. Kuna RS, Kumar A, Wessendorf-Rodriguez KA, Galvez H, Green CR, McGregor GH, et al. Inter-organelle cross-talk supports acetyl-coenzyme A homeostasis and lipogenesis under metabolic stress. Sci Adv. 2023;9(18):eadf0138.
32. Comerford SA, Huang Z, Du X, Wang Y, Cai L, Witkiewicz AK, et al. Acetate Depend Tumors Cell. 2014;159(7):1591–602.
33. Gao X, Lin SH, Ren F, Li JT, Chen JJ, Yao CB, et al. Acetate functions as an epigenetic metabolite to promote lipid synthesis under hypoxia. Nat Commun. 2016;7(1):11960.
34. Mashimo T, Pichumani K, Vemireddy V, Hatanpaa KJ, Singh DK, Sirasanagandla S, et al. Acetate is a Bioenergetic Substrate for Human Glioblastoma and brain metastases. Cell. 2014;159(7):1603–14.
35. Yao L, Jiang L, Zhang F, Li M, Yang B, Zhang F, et al. Acetate promotes *SNAI1* expression by ACSS2-mediated histone acetylation under glucose limitation in renal cell carcinoma cell. Biosci Rep. 2020;40(6):BSR20200382.
36. Li Z, Liu H, He J, Wang Z, Yin Z, You G, et al. Acetyl-CoA synthetase 2: a critical linkage in obesity-Induced Tumorigenesis in Myeloma. Cell Metab. 2021;33(1):78–e937.
37. Zhang S, He J, Jia Z, Yan Z, Yang J. Acetyl-CoA synthetase 2 enhances tumorigenesis and is indicative of a poor prognosis for patients with renal cell carcinoma. Urol Oncol Semin Orig Investig. 2018;36(5):243.e9-243.e20.
38. Murthy D, Attri KS, Shukla SK, Thakur R, Chaika NV, He C, et al. Cancer-associated fibroblast-derived acetate promotes pancreatic cancer development by altering polyamine metabolism via the ACSS2–SP1–SAT1 axis. Nat Cell Biol. 2024;26(4):613–27.
39. Anderson R, Pladna KM, Schramm NJ, Wheeler FB, Kridel S, Pardee TS. Pyruvate dehydrogenase inhibition leads to decreased glycolysis, increased Reliance on Gluconeogenesis and Alternative sources of Acetyl-CoA in Acute myeloid leukemia. Cancers. 2023;15(2):484.
40. Lu Y, Travnickova J, Badonyi M, Rambow F, Coates A, Khan Z, et al. ALDH1A3-acetaldehyde metabolism potentiates transcriptional heterogeneity in melanoma. Cell Rep. 2024;43(7):114406.
41. Long PM, Tighe SW, Driscoll HE, Moffett JR, Namboodiri AMA, Viapiano MS et al. Acetate Supplementation Induces Growth Arrest of NG2/PDGFRα-Positive Oligodendroglioma-Derived Tumor-Initiating Cells. Fillmore H, editor. PLoS ONE. 2013;8(11):e80714.
42. Long PM, Tighe SW, Driscoll HE, Fortner KA, Viapiano MS, Jaworski DM. Acetate supplementation as a Means of Inducing Glioblastoma Stem-Like cell growth arrest: Acetate Induces Glioma Cell Growth Arrest. J Cell Physiol. 2015;230(8):1929–43.

43. Tsen AR, Long PM, Driscoll HE, Davies MT, Teasdale BA, Penar PL, et al. Triacetin-based acetate supplementation as a chemotherapeutic adjuvant therapy in glioma. Int J Cancer. 2014;134(6):1300–10.
44. Garcia JA, Chen R, Xu M, Comerford SA, Hammer RE, Melton SD et al. Acss2/HIF-2 signaling facilitates colon cancer growth and metastasis. Liu C, editor. PLOS ONE. 2023;18(3):e0282223.
45. Sahuri-Arisoylu M, Mould RR, Shinjyo N, Bligh SWA, Nunn AVW, Guy GW, et al. Acetate induces growth arrest in Colon cancer cells through modulation of mitochondrial function. Front Nutr. 2021;8:588466.
46. Lally JSV, Ghoshal S, DePeralta DK, Moaven O, Wei L, Masia R, et al. Inhibition of Acetyl-CoA carboxylase by phosphorylation or the inhibitor ND-654 suppresses lipogenesis and Hepatocellular Carcinoma. Cell Metab. 2019;29(1):174–e1825.
47. Sacco F, Seelig A, Humphrey SJ, Krahmer N, Volta F, Reggio A, et al. Phosphoproteomics reveals the GSK3-PDX1 Axis as a Key Pathogenic Signaling Node in Diabetic islets. Cell Metab. 2019;29(6):1422–e14323.
48. Mir FA, Ullah E, Mall R, Iskandarani A, Samra TA, Cyprian F, et al. Dysregulated metabolic pathways in subjects with obesity and metabolic syndrome. Int J Mol Sci. 2022;23(17):9821.
49. Zhang J, Zhao Y, Xu C, Hong Y, Lu H, Wu J, et al. Association between serum free fatty acid levels and nonalcoholic fatty liver disease: a cross-sectional study. Sci Rep. 2014;4(1):5832.
50. Wang G, Li M, Wang Y, Wang B, Pu H, Mao J, et al. Characterization of differentially expressed and lipid metabolism-related lncRNA-mRNA interaction networks during the growth of liver tissue through rabbit models. Front Vet Sci. 2022;9:998796.
51. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol. 2020;73(1):202–9.
52. Tsochatzis E, Papatheodoridis GV, Manesis EK, Kafiri G, Tiniakos DG, Archimandritis AJ. Metabolic syndrome is associated with severe fibrosis in chronic viral hepatitis and non-alcoholic steatohepatitis. Aliment Pharmacol Ther. 2008;27(1):80–9.
53. Kleiner DE, Makhlouf HR. Histology of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis in adults and children. Clin Liver Dis. 2016;20(2):293–312.
54. Khoonsari M, Mohammad Hosseini Azar M, Ghavam R, Hatami K, Asobar M, Gholami A, et al. Clinical manifestations and diagnosis of nonalcoholic fatty liver disease. Iran J Pathol. 2017;12(2):99–105.
55. Young S, Tariq R, Provenza J, Satapathy SK, Faisal K, Choudhry A, et al. Prevalence and Profile of nonalcoholic fatty liver disease in lean adults: systematic review and Meta-analysis. Hepatol Commun. 2020;4(7):953–72.
56. Williams CD, Stengel J, Asike MI, Torres DM, Shaw J, Contreras M, et al. Prevalence of nonalcoholic fatty liver Disease and Nonalcoholic Steatohepatitis among a largely middle-aged Population utilizing Ultrasound and Liver Biopsy: a prospective study. Gastroenterology. 2011;140(1):124–31.
57. Pouwels S, Sakran N, Graham Y, Leal A, Pintar T, Yang W, et al. Non-alcoholic fatty liver disease (NAFLD): a review of pathophysiology, clinical management and effects of weight loss. BMC Endocr Disord. 2022;22(1):63.
58. Sookoian S, Pirola CJ, Valenti L, Davidson NO. Genetic pathways in nonalcoholic fatty liver disease: insights from systems Biology. Hepatology. 2020;72(1):330–46.
59. Zhao S, Jang C, Liu J, Uehara K, Gilbert M, Izzo L, et al. Dietary fructose feeds hepatic lipogenesis via microbiota-derived acetate. Nature. 2020;579(7800):586–91.
60. Sellmann C, Priebs J, Landmann M, Degen C, Engstler AJ, Jin CJ, et al. Diets rich in fructose, fat or fructose and fat alter intestinal barrier function and lead to the development of nonalcoholic fatty liver disease over time. J Nutr Biochem. 2015;26(11):1183–92.
61. Jang C, Hui S, Lu W, Cowan AJ, Morscher RJ, Lee G, et al. The small intestine converts Dietary Fructose into glucose and Organic acids. Cell Metab. 2018;27(2):351–e3613.
62. Yenilmez B, Kelly M, Zhang GF, Wetoska N, Ilkayeva OR, Min K, et al. Paradoxical activation of transcription factor SREBP1c and de novo lipogenesis by hepatocyte-selective ATP-citrate lyase depletion in obese mice. J Biol Chem. 2022;298(10):102401.
63. Nassir FNAFLD. Mechanisms, treatments, and biomarkers. Biomolecules. 2022;12(6):824.
64. Muñoz AE, Pollarsky F, Marino M, Cartier M, Míguez C, Vázquez H, et al. Safety of chronic simvastatin treatment in patients with decompensated cirrhosis: many adverse events but no Liver Injury. Dig Dis Sci. 2021;66(9):3199–208.
65. Zhou T, Cao L, Du Y, Qin L, Lu Y, Zhang Q, et al. Gypenosides ameliorate high-fat diet-induced nonalcoholic fatty liver disease in mice by regulating lipid metabolism. PeerJ. 2023;11:e15225.
66. World Health Organization (WHO). Obesity and Overweight. 2024 [cited 2024 Jul 17]. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
67. Pereira MA, Kartashov AI, Ebbeling CB, Van Horn L, Slattery ML, Jacobs DR, et al. Fast-food habits, weight gain, and insulin resistance (the CARDIA study): 15-year prospective analysis. Lancet. 2005;365(9453):36–42.
68. Romero-Ibarguengoitia ME, Vadillo-Ortega F, Caballero AE, Ibarra-González I, Herrera-Rosas A, Serratos-Canales MF et al. C Fürnsinn editor 2018 Family history and obesity in youth, their effect on acylcarnitine/aminoacids metabolomics and non-alcoholic fatty liver disease (NAFLD). Structural equation modeling approach. PLoS ONE 13;2:e0193138.
69. Wu Y, Duan H, Tian X, Xu C, Wang W, Jiang W, et al. Genetics of obesity traits: a Bivariate Genome-Wide Association Analysis. Front Genet. 2018;9:179.
70. Bäckhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, et al. The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci. 2004;101(44):15718–23.
71. Ren Y, Huang P, Huang X, Zhang L, Liu L, Xiang W, et al. Alterations of DNA methylation profile in peripheral blood of children with simple obesity. Health Inf Sci Syst. 2024;12(1):26.
72. Chen C, Chen W, Ding H, Wu P, Zhang G, Xie K, et al. High-fat diet-induced gut microbiota alteration promotes lipogenesis by butyric acid/miR-204/ACSS2 axis in chickens. Poult Sci. 2023;102(9):102856.
73. Chen C, Chen W, Ding H, Zhang G, Xie K, Zhang T. Integrated Metabolomic and Transcriptomic Analysis reveals potential gut-liver crosstalks in the lipogenesis of chicken. Animals. 2023;13(10):1659.
74. Alli Shaik A, Qiu B, Wee S, Choi H, Gunaratne J, Tergaonkar V. Phosphoprotein network analysis of white adipose tissues unveils deregulated pathways in response to high-fat diet. Sci Rep. 2016;6(1):25844.
75. Garrido-Sánchez L, Vendrell J, Fernández-García D, Ceperuelo-Mallafré V, Chacón MR, Ocaña-Wilhelmi L et al. De Novo Lipogenesis in Adipose Tissue Is Associated with Course of Morbid Obesity after Bariatric Surgery. Rouet P, editor. PLoS ONE. 2012;7(2):e31280.
76. Chen N, Zhao M, Wu N, Guo Y, Cao B, Zhan B, et al. ACSS2 controls PPARγ activity homeostasis to potentiate adipose-tissue plasticity. Cell Death Differ. 2024;31(4):479–96.
77. Sakakibara I, Fujino T, Ishii M, Tanaka T, Shimosawa T, Miura S, et al. Fasting-Induced Hypothermia and Reduced Energy Production in mice lacking Acetyl-CoA synthetase 2. Cell Metab. 2009;9(2):191–202.
78. American Diabetes Association. Diagnosis and classification of diabetes Mellitus. Diabetes Care. 2014;37(Supplement1):S81–90.
79. Li D, Zhang L, Yang P, He Y, Zhou T, Cheng X, et al. Sodium benzoate induces pancreatic inflammation and β cell apoptosis partially via benzoylation. Ecotoxicol Environ Saf. 2024;270:115877.
80. Zhou T, Xu H, Cheng X, He Y, Ren Q, Li D et al. Sodium Butyrate Attenuates Diabetic Kidney Disease Partially via Histone Butyrylation Modification. Caccamo D, editor. Mediators Inflamm. 2022;2022:1–16.
81. Huang C, Huang B, bin, Niu J min, Yu Y, Qin X, yun, Yang Y et al. li,. Global mRNA and Long Non-Coding RNA Expression in the Placenta and White Adipose Tissue of Mice Fed a High-Fat Diet During Pregnancy. Cell Physiol Biochem. 2018;50(6):2260–71.
82. Han S, Akiyama TE, Previs SF, Herath K, Roddy TP, Jensen KK, et al. Effects of small interfering RNA-mediated hepatic glucagon receptor inhibition on lipid metabolism in db/db mice. J Lipid Res. 2013;54(10):2615–22.
83. Wopereis S, Radonjic M, Rubingh C, Van Erk M, Smilde A, Van Duyvenvoorde W, et al. Identification of prognostic and diagnostic biomarkers of glucose intolerance in ApoE3Leiden mice. Physiol Genomics. 2012;44(5):293–304.
84. Tian Z, Liang M. Renal metabolism and hypertension. Nat Commun. 2021;12(1):963.
85. Mukhi D, Li L, Liu H, Doke T, Kolligundla LP, Ha E, et al. ACSS2 gene variants determine kidney disease risk by controlling de novo lipogenesis in kidney tubules. J Clin Invest. 2024;134(4):e172963.
86. Miao N, Yin F, Xie H, Wang Y, Xu Y, Shen Y, et al. The cleavage of gasdermin D by caspase-11 promotes tubular epithelial cell pyroptosis and urinary IL-18 excretion in acute kidney injury. Kidney Int. 2019;96(5):1105–20.
87. Lu J, Hou Y, Liu SX, Jin B, Liu J, Li N, et al. Acetyl-CoA synthetase 2 induces pyroptosis and inflammation of renal epithelial tubular cells in sepsis-induced acute kidney injury by upregulating the KLF5/NF-κB pathway. Cell Commun Signal. 2024;22(1):187.

88. Li L, Xiang T, Guo J, Guo F, Wu Y, Feng H, et al. Inhibition of ACSS2-mediated histone crotonylation alleviates kidney fibrosis via IL-1β-dependent macrophage activation and tubular cell senescence. Nat Commun. 2024;15(1):3200.
89. Afkarian M, Sachs MC, Kestenbaum B, Hirsch IB, Tuttle KR, Himmelfarb J, et al. Kidney disease and increased mortality risk in type 2 diabetes. J Am Soc Nephrol. 2013;24(2):302–8.
90. Lu J, Li XQ, Chen PP, Zhang JX, Liu L, Wang GH, et al. Activation of acetyl-CoA synthetase 2 mediates kidney injury in diabetic nephropathy. JCI Insight. 2023;8(20):e165817.
91. Ligthart S, Vaez A, Võsa U, Stathopoulou MG, De Vries PS, Prins BP, et al. Genome analyses of > 200,000 individuals identify 58 Loci for Chronic Inflammation and highlight pathways that Link inflammation and Complex disorders. Am J Hum Genet. 2018;103(5):691–706.
92. Püschel GP, Klauder J, Henkel J, Macrophages L-G, Inflammation. Insulin Resistance and hyperinsulinemia: a mutual ambiguous relationship in the development of metabolic diseases. J Clin Med. 2022;11(15):4358.
93. Yadav SS, Nair RR, Singh K, Editorial. Cause or effect: role of inflammation in metabolic disorder. Front Endocrinol. 2024;15:1359605.
94. Gasmi A, Noor S, Menzel A, Doşa A, Pivina L, Bjørklund G. Obesity and insulin resistance: associations with chronic inflammation, genetic and epigenetic factors. Curr Med Chem. 2021;28(4):800–26.
95. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest. 2003;112(12):1796–808.
96. Harman-Boehm I, Blüher M, Redel H, Sion-Vardy N, Ovadia S, Avinoach E, et al. Macrophage infiltration into Omental *Versus* Subcutaneous Fat across different populations: Effect of Regional Adiposity and the comorbidities of obesity. J Clin Endocrinol Metab. 2007;92(6):2240–7.
97. Liu C, Feng X, Li Q, Wang Y, Li Q, Hua M, Adiponectin. TNF-α and inflammatory cytokines and risk of type 2 diabetes: a systematic review and meta-analysis. Cytokine. 2016;86:100–9.
98. Alzamil H. Elevated serum TNF- α is related to obesity in type 2 diabetes Mellitus and is Associated with Glycemic control and insulin resistance. J Obes. 2020;2020:1–5.
99. Mounika N, Mungase SB, Verma S, Kaur S, Deka UJ, Ghosh TS et al. Inflammatory Protein Signatures as Predictive Disease-Specific Markers for Non-Alcoholic Steatohepatitis (NASH). Inflammation. 2024 Apr 27 [cited 2024 May 11]; Available from: https://link.springer.com/https://doi.org/10.1007/s10753-024-02035-0
100. Im SS, Yousef L, Blaschitz C, Liu JZ, Edwards RA, Young SG, et al. Linking lipid metabolism to the Innate Immune Response in Macrophages through sterol Regulatory element binding Protein-1a. Cell Metab. 2011;13(5):540–9.
101. Fernandez S, Viola JM, Torres A, Wallace M, Trefely S, Zhao S, et al. Adipocyte ACLY facilitates Dietary Carbohydrate handling to maintain metabolic homeostasis in females. Cell Rep. 2019;27(9):2772–e27846.
102. Verberk SGS, Van Der Zande HJP, Baardman J, De Goede KE, Harber KJ, Keuning ED, et al. Myeloid ATP citrate lyase regulates macrophage inflammatory responses in Vitro without altering Inflammatory Disease outcomes. Front Immunol. 2021;12:669920.
103. Kendrick SFW, O'Boyle G, Mann J, Zeybel M, Palmer J, Jones DEJ, et al. Acetate, the key modulator of inflammatory responses in acute alcoholic hepatitis. Hepatology. 2010;51(6):1988–97.
104. Márquez S, Fernández JJ, Mancebo C, Herrero-Sánchez C, Alonso S, Sandoval TA, et al. Tricarboxylic acid cycle activity and remodeling of glycerophosphocholine lipids support cytokine induction in response to fungal patterns. Cell Rep. 2019;27(2):525–e5364.
105. Boonpethkaew S, Meephansan J, Jumlongpim O, Tangtanatakul P, Soonthornchai W, Wongpiyabovorn J, et al. Transcriptomic profiling of Peripheral Edge of lesions to elucidate the pathogenesis of Psoriasis Vulgaris. Int J Mol Sci. 2022;23(9):4983.
106. Jung MK, Kwak JE, Shin EC. IL-17A-Producing Foxp3 $^{+}$ Regulatory T cells and human diseases. Immune Netw. 2017;17(5):276.
107. Fiyouzi T, Pelaez-Prestel HF, Reyes-Manzanas R, Lafuente EM, Reche PA. Enhancing Regulatory T Cells to treat Inflammatory and Autoimmune diseases. Int J Mol Sci. 2023;24(9):7797.
108. Hao F, Tian M, Zhang X, Jin X, Jiang Y, Sun X, et al. Butyrate enhances CPT1A activity to promote fatty acid oxidation and iTreg differentiation. Proc Natl Acad Sci. 2021;118(22):e2014681118.
109. Daïen CI, Tan J, Audo R, Mielle J, Quek LE, Krycer JR, et al. Gut-derived acetate promotes B10 cells with antiinflammatory effects. JCI Insight. 2021;6(7):e144156.
110. Fillatreau S, Sweenie CH, McGeachy MJ, Gray D, Anderton SM. B cells regulate autoimmunity by provision of IL-10. Nat Immunol. 2002;3(10):944–50.
111. Mauri C, Gray D, Mushtaq N, Londei M. Prevention of Arthritis by Interleukin 10–producing B cells. J Exp Med. 2003;197(4):489–501.
112. Huang Y, Yang L, Hui R, Chang Y, Yang Y, Yang C, et al. Relationships between obesity and the clinical severity of psoriasis in Taiwan. J Eur Acad Dermatol Venereol. 2010;24(9):1035–9.
113. Dhaher SA, Hilfi NZ, Abdullah MA. Non-alcoholic Fatty Liver Disease Among Iraqi Patients With Psoriasis: A Case-Control Study. Cureus. 2024 Apr 2 [cited 2024 May 25]; Available from: https://www.cureus.com/articles/240271-non-alcoholic-fatty-liver-disease-among-iraqi-patients-with-psoriasis-a-case-control-study
114. Chavez-Tapia NC, Sanchez-Jimenez BA, Vidaña-Perez D, Corrales-Rosas B, Balderas-Garces B, Vera-Izaguirre D et al. Predictors for liver fibrosis in non-alcoholic patients with psoriatic diseases: A multicenter cross sectional-study. Karimi-Sari H, editor. PLOS ONE. 2024;19(4):e0290632.
115. Lowes MA, Kikuchi T, Fuentes-Duculan J, Cardinale I, Zaba LC, Haider AS, et al. Psoriasis Vulgaris lesions Contain Discrete populations of Th1 and Th17 T cells. J Invest Dermatol. 2008;128(5):1207–11.
116. Henriet E, Abdallah F, Laurent Y, Guimpied C, Clement E, Simon M, et al. Targeting TGF-β1/miR-21 pathway in Keratinocytes reveals Protective effects of Silymarin on Imiquimod-Induced Psoriasis Mouse Model. JID Innov. 2023;3(3):100175.
117. Zhang L, McCabe T, Condra JH, Ni YG, Peterson LB, Wang W, et al. An Anti-PCSK9 antibody reduces LDL-Cholesterol on top of a statin and suppresses hepatocyte SREBP-Regulated genes. Int J Biol Sci. 2012;8(3):310–27.
118. Hu XQ, Song YN, Wu R, Cai FF, Zhang Y, Peng JH, et al. Metabolic mechanisms of Fuzheng-Huayu formula against liver fibrosis in rats. J Ethnopharmacol. 2019;238:111888.
119. Liang Y, Yi L, Deng P, Wang L, Yue Y, Wang H, et al. Rapamycin antagonizes cadmium-induced breast cancer cell proliferation and metastasis through directly modulating ACSS2. Ecotoxicol Environ Saf. 2021;224:112626.
120. Perets R, Geva R, McKean M, Goutopoulos A, Erez O, Phadnis M, et al. Phase 1 first-in-human trial of MTB-9655, the first oral inhibitor of ACSS2, in patients with advanced solid tumors. J Clin Oncol. 2022;40(16suppl):e20609–20609.
121. Study of MTB. -9655, an Inhibitor of ACSS2, in Patients With Advanced Solid Tumors. [cited 2024 Jul 17]. Available from: https://clinicaltrials.gov/study/NCT04990739

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