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DYSREGULATION OF LONG-CHAIN ACYL-CoA SYNTHETASES IN CANCER AND THEIR TARGETING STRATEGIES IN ANTICANCER THERAPY

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ABSTRACT: Cancer is a leading cause of death worldwide, and the number of cases globally continues to increase. Cancer is caused by certain changes in genes that are involved in controlling cell functions and cell division. Notably, metabolic dysregulation is one the hallmarks of cancer, and increases in fatty acid metabolism have been demonstrated to promote the growth and survival of a variety of cancers. In human, fatty acids either can be breakdown into acetyl-CoA through catabolic metabolism and aid in ATP generation or in the anabolic metabolism they can incorporate into triacylglycerol and phospholipid. Importantly, both of these pathways need activation of fatty acids, and the key players in this activation of fatty acids are the long-chain acyl-CoA synthetases (ACSLs) that are commonly dysregulated in cancer and associated with oncogenesis and survival. Therefore, it provides a rationale to target ACSLs in cancer. This review summarizes the current understanding of long-chain acyl-CoA synthetases in cancer and their targeting opportunities.

KEYWORDS: Acyl-CoA synthetases, cancer, fatty acid, lipid metabolism.

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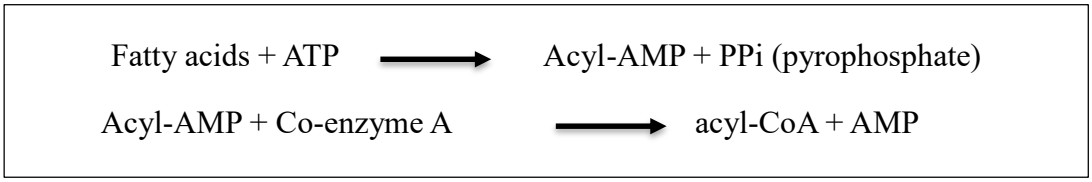
1. INTRODUCTION

Fatty acids are the crucial nutrient in mammalian, which serve as building blocks of the body. They can be obtained from dietary intake or derived from *de nono* synthesis. Fatty acids participate in cellular metabolism and signaling to maintain physiological functions. However, dysregulation of

fatty acids metabolism triggers several psychological disorders, such as diabetes mellitus and carcinogenesis [1, 2]. In multiple cancers, including breast cancer, colorectal cancer, and non-small cell lung cancer, fatty acids levels in serum act as a tumor prognostic biomarker and can predict the response to therapy [3-5]. Indeed, multiple cancer types increase the uptake of extracellular fatty acids [6]. There are 26 kinds of acyl-coenzyme A (acyl-CoA) synthetases (ACS), in mammalian, which can be divided into very long-chain acyl-CoA synthases (ACSVLs), long-chain acyl-CoA synthases (ACSLs), medium-chain acyl-CoA synthases (ACSMs) and short-chain acyl CoA syntheses (ACSSs) [7-9]. The members of ACSs catalyze a two-step reaction:



The ACSLs family comprises five isoenzymes, includes ACSL1, ACSL3, ACSL4, ACSL5, and ACSL6. It has been reported that ACSLs are a group of enzymes that play an essential role in lipid metabolism, including *de novo* lipid synthesis, fatty acid degradation, and membrane remodeling, which catalyze the esterification of C12-C20 fatty acids [6, 7]. These five isoforms have specific roles in the activation of fatty acids, and they have particular substrate preferences. For example, oleate and linoleate specific for ACSL1, myristate and palmitate specific for ACSL3, and arachidonic acids for ACSL4 [2, 7, 10]. Recently, several studies found that dysregulation of ACSLs function in cancer tissues and may have a role in cancer. The purpose of this review is to summarize the role of ACSLs in cancer and therapeutic intervention by targeting fatty acid metabolic enzymes.

2. STRUCTURE AND SUBCELLULAR DISTRIBUTION OF ACSLs

ACSs belong to the superfamily of adenylate-forming enzymes, where ACSLs are the members of ACSs subfamily. ACSLs are homologous in their sequences. Although the five ACSL members are similar based on their gene structure, they can be divided into two subgroups, ACSL1 / ACSL5 / ACSL6 and ACSL3 / ACSL4 [11]. They also share the homology with luciferase enzymes and non-ribosomal peptide synthetase adenylation domains [7, 12]. ACSLs structure is very close to luciferase, one amino acid (serine) change can convert an ACSLs to a luciferase [13]. Importantly, Kochan *et al.* revealed the crystal structure of ACSs and found the importance of divalent magnesium ion in mediating interactions with the ATP phosphoryl groups, and the role of the arginine-glycine salt bridge in the domain rearrangement [14]. The location of ACSLs in the human body is not fully elucidated. However, several studies revealed that ACSL1 is localized in skeletal muscle, liver, mitochondria, heart, brain, and adipose tissue [2]. ACSL3 mainly localized in the endoplasmic reticulum and liver cells. ACSL4 is widely distributed in the plasma membrane, peroxisomes, endoplasmic region, and in many secretory pathways heart [1, 15]. ACSL5 locates in the lung, mucosa, testis, and ovary, and ACSL6 is highly present in the brain [16, 17]. The

subcellular location of ACSLs may dictate the function of specific ACSLs, such as ACSL1, ACSL2, and ACSL4 are located in the endoplasmic reticulum and contributes glycerolipid synthesis and ω-oxidation. In contrast, in mitochondria ACSL2, ACSL4, ACSL5 have been found involved in fatty acids synthesize and β-oxidation [1, 18].

3. PHYSIOLOGICAL ROLES OF ACSLs

ACSLs required for rapidly growing cells. ACSLs mainly play an essential role in lipid metabolism, including *de novo* lipid synthesis and fatty acid oxidation. Tissue-specific studies of ACSLs unveiled the function of ACSLs more specifically. For instance, ACSL1 has a crucial part in fatty acids oxidation, knockdown of ACSL1 from liver adipose, heart, and skeletal muscle significantly reduced fatty acid oxidation [19-21]. Besides, ACSL4 is an essential component of ferroptosis, knockdown, or pharmacological inhibition of ACSL4 showed marked resistance to ferroptosis [22]. Importantly, ACSL4 expression is higher in the brain, and the deletion of ACSL4 results in several mental difficulties, which suggested that ACSL4 may have an important role in brain function [23]. ACSL5 knockout mice showed a decrease in fatty acid activation [16]. Knocking down of ACSL3 and ACSL1 diminished triacylglycerol [19, 24]. Several overexpression studies also found similar finding like knockdown studies, such as overexpression of ACSL1 in hepatocytes increased fatty acid oxidation and ACSL5 overexpression inclined triacylglycerol levels [25, 26]. Moreover, ACSLs have a role in transcriptional regulation. For instance, silencing ACSL3 downregulated peroxisome proliferator-activated receptor-γ expression in hepatocytes [24]. Altogether suggests that ACSLs have an important function in fatty acid metabolism.

4. REGULATION OF ACSLs IN CANCER

In recent years ACSLs have gotten much interest. In many cancers, ACSLs are dysregulated and related with poor survival. ACSLs also responsible for carcinogenesis and cancer development. Several studies found that ACSLs induced government cell proliferation, which is the main hallmark of cancer. Knocked down of specific ACSLs reduced the proliferation of cancer cells. For instance, in colon cancer cells deficient of ACSLs reduced their proliferation potential [27]. Silencing of ACSL4 in hepatocellular carcinoma cells also reduced proliferative potential [28]. On the other hand, overexpression of ACSLs accelerates hepatocellular tumor growth and metastasis [29]. Besides, ACSLs can meet the increasing demand of lipids for the cancer cells. ACSL1 and ACSL4 are upregulated in different and proposed that the lipid anabolism and catabolism activity of these ACSLs are helpful for tumor progression [27, 30]. Moreover, ACSLs also have important roles in glucose metabolism, apoptosis, and metastasis. On the other hand, ACSLs also have an anti-tumor role in several cancers. The following chapter brings together the impacts of specific ACSLs in cancer.

4.1. ACSL1

ACSL1 upregulated in multiple cancer types, including liver, myeloma, breast, and colon cancer,

and upregulation of ACSL1 associated with poor survival [31, 32]. In colorectal cancer cell lines overexpression of ACSL1 enhanced invasion from epithelial to mesenchymal transition and glycolysis, and knockdown of this decreased the proliferation and metastasis in compared to the empty vector [33, 34]. The knockdown of ACSL1 in breast cancer cell lines reduced colony formation and cell viability [34]. However, in non-small cell lung cancer cell lines, deficient of ACSL1 enhanced proliferation and invasiveness [34]. In estrogen positive and negative breast cancer, the mRNA level of ACSL1 is upregulated and correlated with poor survival. In lung cancer, ACSL1 is downregulated, and the silencing of ACSL1 increased the invasiveness of lung cancer [34]. Therefore, it is suggested that ACSL1 may have an anti-tumor effect in lung cancer, although it promotes colorectal cancer metastasis.

4.2. ACSL3

ACSL3 is also found to be highly expressed in many tumors. However, the expression decreased in metastatic prostate cancer [35]. The role of ACSL3 in cancer is complicated. In some tumors, the overexpression of ACSL3 correlates with poor prognosis [36, 37]. On the other hand, reduction ACSL3 increases recurrences and metastasis [29]. Padanad *et al.* found that fatty acid oxidation by ACSL3 is required for lung tumorigenesis in adjuvant chemotherapy-treated patients [37]. However, in triple-negative breast cancer, ACSL3 can interact with CUB domain-containing protein 1 that decreases fatty acid oxidation and reduced lipid droplets and enhances prognosis [38]. Moreover, in castration-resistant prostate cancer, ACSL3 increased intratumor steroidogenesis that favored prostrate tumor growth [39]. In melanoma cancer, ACSL3 correlated with poor prognosis, and it increased the levels of lipid droplets [34]. The reason behind this is not clear, but a high amount of lipid droplet levels in melanoma tumor microenvironment favored resistance to therapy as well as proliferation. ACSL3 regulates intratumoral lipid synthesis, which makes ACSL3 an important factor that can modules melanoma tumor growth. In lung cancer, ACSL3 expression increased with the later stage of the tumor. It also involved in KRAS-mediated tumorigenesis [37]. Altogether, ACSL3 has tumorigenesis and tumor-inhibiting ability depending on tumor types and tumor microenvironment. Therefore, targeting ACSL3 in cancer therapy needs further study with consideration of tumor types.

4.3. ACSL4

ACSL4 is one of the important members of ACSLs, which associated with uncontrolled cell growth and facilitates tumor invasion. ACSL4 upregulated in different types of tumors, such as breast, liver, colon, and gastric cancer [6]. Several studies have shown that overexpression of ACSL4 associated with poor survival. Moreover, ACSL4 plays oncogenic role in different cancers. In estrogen receptor-expressing breast cancer ACSL4 is necessary for invasiveness [40]. *In vitro* knockdown of ACSL4 from multiple cancer cell lines as well as in xenograft tumor models shown a reduction in tumor growth, whereas overexpression of ACSL4 shown opposite, enforced expression of ACSL4

in MCF7 cells increased metastasis and migration [28, 40]. Importantly, ACSL4 levels can be used as a prognostic biomarker in many cancer, as overexpression of ACSL4 increased proliferation and resistance to therapy [41]. In castration-resistant prostate cancer (CRPC), Xinyu *et al.* found that ACSL4 was highly expressed compared with prostate cancer. It also upregulated pathways associated with CRPC growth, and they suggested ACSL4 might promote prostate cancer towards CPRC [29]. ACSL4 also facilitates fatty acid synthesis and fatty acid oxidation, which is an important metabolic source of T cell, as T cell used fatty acid oxidation as an alternative source of energy metabolites [42]. Of note, apoptosis is important in immune surveillance that can kill or remove mutant or damaged cells, and reduces the chances of tumorigenesis. However, overexpression of ACSL4 inhibits the initiation of apoptosis due to its preferences toward arachidonic acid, which responsible for the initiation of apoptosis [43]. Which suggested that ACSL4 has a function in cancer cell survival. However, ACSL4 has a crucial role in ferroptosis (another form of programmed cell death). It dictates the ferroptosis process [22]. Taken together, ACSL4 may promote tumor growth and function as tumor promoter enzyme. However, it can induce ferroptosis and may help in T cell-mediated cytotoxicity, which is an area of interest need to be elucidated.

4.4. ACSL5

ACSL5 mainly localized in mitochondria. It also localized in adipose tissue, lung, and liver. It supports fatty acid oxidation and fatty acids synthesis, knockdown of ACSL5 can increase energy expenditure and delay fat absorption [44]. In some cancer expression of ACSL5 was downregulated as well as it was upregulated in different cancer, such as in breast and colon cancer ACSL5 was downregulated, whereas ACSL5 was upregulated in bladder cancer [1]. ACSL5 has a cancer-inhibiting role, lower expression of ACSL5 in breast cancer increased tumor growth, and worsen prognosis [6]. Other studies showed that the downregulation of ACSL5 associated with poor survival. On the contrary, other studies found that ACSL5 promoted glioma cell growth and in gastric cancer, and ACSL5 induced resistance of fibroblast growth factor 2 inhibitors [1, 45]. In liver cancer, ACSL5 expression was downregulated, however the role of ACSL5 in liver cancer remains obscure. Moreover, under extracellular acidosis, ACSL5 increased glioma cell survival, and knockdown of ACSL5 cell viability was decreased, which suggested that ACSL5 is necessary for glioma cell survival and ACSL5 can be targeted in therapy [46]. Furthermore, in colorectal cancer Shihua *et al.* found that ACSL5 was upregulated, especially in patients with poorly differentiated tumor, and knockdown of ACSL5 reduced the growth and invasiveness of colorectal cancer cells. However, ectopic expression of ACSL5 inhibited cell apoptosis and enhanced cell migration [47]. Taken together, ACSL5 has tumor-inhibiting function in breast cancer, but it can promote the growth of glioma and colorectal cancer.

4.5. ACSL6

Few studies have been conducted on ACSL6 regarding cancers. ACSL6 mainly involved in saturated and unsaturated fatty acids metabolism in humans. Bioinformatics study showed that ACSL6 highly expressed in cancer tissues compared to healthy tissue [34]. In the liver, ACSL6 can increase the accumulation of lipid droplets that can initiate the tumorigenesis of hepatocellular carcinoma [48]. Thus, ACSL6 can contribute to liver cancer initiation. However, in blood cancer, ACSL6 functioned as a tumor suppressor. In leukemia, a low level of ACSL6 favored poor patient survival [34]. Further studies are needed to elucidate the role of ACSL6 in cancer.

5. TARGETING ACSLs IN CANCER

ACSLs are dysregulated in multiple cancers, and ACSLs are necessary for many tumors' initiation. These suggest ACSLs could be a potential target in cancer therapy. In colorectal cancer, silencing ACSL1 by shRNA showed reduced tumor proliferation and metastasis. ACSL1 also have a function in glycolysis, thus inhibiting ACSL1 and glycolysis in colorectal cancer may have synergistic antitumor effects [27, 34]. Moreover, stearoyl-CoA desaturase (SCD1) inhibitors can inhibit the formation of tumors that rely on *de novo* fatty acids synthesis. Thus, the tumors which depend on *de novo* fatty acids synthesis could be targeted by a combination of ACSLs and SCD1 inhibitors because ACSLs are contributing de novo fatty acids synthesis [49]. As we described in 4.2. section ACSL3 also upregulated in many cancers and promotes tumor progression by maintaining fatty acid oxidation, so inhibiting ACSL3 could be potential with fatty acid oxidation inhibitor, such as etomoxir. Moreover, fatty acid oxidation by ACSL3 is necessary for mutant KRAS mediated lung cancer. Thus, inhibiting KRAS also could be a potential target with ACSL3. Notably, ACSL4 is one of the crucial targets in ACSLs mediated cancer therapy. Several studies showed that inhibiting ACSL4 pharmacologically as well as knocking down has led to having a potential anti-tumor effect. For example, knockdown of ACSL4 from colorectal cancer, prostate cancer, hepatocellular cancer and breast cancer cell lines have shown significant decreased in cell proliferation, cell viability, and invasiveness [6, 18, 27]. Besides, pharmacological inhibition of ACSL4 by triacin-c with SCD1 inhibition improved cancer therapy [33]. ACSL5 also upregulated in different cancer, however ACSL5 may have anti-tumor effects, but targeting ACSL5 in glioma could be potential because glioma cell survival and metastasis are dependent on ACSL5 [46]. ACSL6 is not well studied ACSLs in cancer. Yet, a growing body of ideas supported that ACSL6 may have opposite roles in cancer. Altogether, targeting ACSLs in cancer is tricky because ACSLs have a role in tumor inhibition as well as in tumor progression. Thus, targeting ACSLs with the consideration of tumor types as well as combine with other therapeutic strategies might open a new potential approach in cancer therapy.

2. CONCLUSION

Metabolic dysregulation is a hallmark of cancer, and dysregulation of fatty acids metabolism is associated with multiple cancer types. Importantly, ACSLs are the main metabolizing enzymes of fatty acids in human, which are commonly dysregulated in cancer and responsible for tumorigenesis. Besides, targeting ACSLs in cancers have shown potential efficacy in anticancer therapy. Therefore, identifying potential targets of ACSLs with effective combination strategies may help in cancer treatment. However, in some cancers, ACSLs have opposite roles, and the underlying mechanism of ACSLs-mediated tumorigenesis not fully elucidated. Further studies are needed to improve our understanding of the role of ACSLs in cancer.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this research are available within the article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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