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Research Progress of ACSLs and Breast Cancer

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Abstract: Long-chain acyl-CoA synthase (ACSL) is a key enzyme that catalyzes the activation of fatty acids and plays an important role in the metabolism of fatty acids. ACSL includes five different subtypes, and the expression of a single ACSL subtype can change the distribution and quantity of fatty acids in cells, which in turn will change the expression of ACSLs in cells. ACSL is abnormally expressed in many types of tumors, and has complex functions in promoting tumor cell proliferation or apoptosis and affecting tumor progression. ACSL regulates tumor progression through different signal transduction pathways and molecular mechanisms, and its abnormal expression has certain influence on tumor differentiation, tumor prognosis and recurrence, which is expected to become a new marker and therapeutic target. In recent years, the incidence and mortality of breast cancer have increased significantly, and breast cancer patients in China are becoming younger. This article reviews the related research on ACSL and breast cancer, and understands the exact role of ACSL in breast cancer and the molecular mechanism involved, which can provide ideas for finding new targets for breast cancer diagnosis and treatment and developing new strategies for gene therapy.

1. Introduction

Cancer is one of the leading causes of death worldwide. Studies have shown that the disorder of lipid metabolism contributes to the progress of cancer[1]. The enhancement of lipid biosynthesis is closely related to the occurrence of tumors[2]. Fatty acid is the main energy source of mammals. Under aerobic conditions, fatty acids in human body can be decomposed into CO2 and H2O, and a large amount of energy is released in the form of ATP for the body to use. In tumor cells, the supply of cellular fatty acids is highly dependent on ab initio synthesis, but fatty acids must form bioactive fatty acyl-CoA to enter the relevant metabolic pathway to produce ATP, and fatty acid activation needs to be esterified by long-chain fatty acyl-CoA synthetase (ACSLs). Evidence has shown that ACSLs is an essential enzyme responsible for fatty acid metabolism[3], which is closely related to the occurrence and development of many diseases. Many studies have found that ACSLs is closely related to the occurrence and development of tumors. There are many differences in the expression of ACSLs in different tumor diseases, and it plays an important regulatory role in the proliferation,

apoptosis, migration and invasion of tumor cells. At the same time, the expression of ACSLs has certain influence on the differentiation, prognosis and recurrence of tumor tissues. These results indicate that lipid metabolism mediators are newly discovered molecular targets for inducing selective death of tumor cells. In this paper, the related literatures about ACSLs and breast cancer in recent years are analyzed and summarized, so as to provide new ideas for the treatment of breast cancer.

2. Overview of Long-Chain Acyl-CoA Synthetase Family (ACSLs)

Acyl-CoA synthetase family has five members, including short-chain acyl-CoA synthetase, medium-chain acyl-CoA synthetase, long-chain acyl-CoA synthetase (ACSL), bubble gum acyl-CoA synthetase and very long-chain acyl-CoA synthetase. Each member has unique substrate preference and enzyme activity in different cell locations. The length of carbon chain of fatty acid species determines the substrate specificity of different acyl-CoA synthetases (ACS). Long-chain acyl-coenzyme A synthetase (ACSLs) prefers specific substrates of fatty acids with chain length of 12 to 20 carbon atoms. The five subtypes of ACSLs in mammals are ACSL1, 3, 4, 5 and 6, respectively[4]. ACSL1 is expressed in endoplasmic reticulum and mitochondrial membrane of hepatocytes, plasma membrane and lipid droplets of adipocytes[5], which may be related to the absorption of intracellular fatty acids. ACSL3 mainly exists in lipid droplets in cells[6]. Lipid droplets are the main organelles for storing neutral lipids, which play an important role in storing energy and providing lipid molecules. ACSL3 promotes the formation of lipid droplets and is conducive to maintaining lipid homeostasis. ACSL4 is mainly expressed in peroxisome and mitochondrial membrane, and participates in the transport of cholesterol from endoplasmic reticulum to mitochondria[7]. The expression of ACSL4 will affect the proliferation, migration and invasion ability of cancer cells and the apoptosis of cancer cells[8,9]. ACSL5 is expressed in mitochondria and endoplasmic reticulum, and plays a regulatory role in mitochondrial energy metabolism. ACSL5 can induce cell apoptosis and promote cell survival[10,11]. ACSL6 exists in plasma membrane and shows high activity with C16-C20 saturated and polyunsaturated fatty acids[12]. Wei-Ching Chen et al [13] found that ACSL1 may play a certain carcinogenic role in breast cancer. Through analysis and experiment, they found that the tumorigenicity of ACSL1 in lung cancer cells increased, on the contrary, ACSL1 was down-regulated in breast cancer cell lines, thus inhibiting the proliferation and metastasis of breast cancer cells. The high level of ACSL3 in melanoma patients indicates a poor prognosis. On the contrary, the high expression of ACSL3 in ovarian cancer patients indicates a better prognosis. The high expression of ACSL4 in colorectal cancer patients indicates a poor prognosis, but at the same time ACSL4 has a good prognosis in breast cancer and lung cancer. The high expression of ACSL5 indicates a good prognosis of breast cancer, ovarian cancer and lung cancer. The expression of ACSL6 indicates that the prognosis of acute myeloid leukemia is poor. Generally speaking, different members of ACSLs have certain relationships with different tumors.

3. ACSLS and Breast Cancer

Breast cancer is a phenomenon that breast epithelial cells proliferate out of control under the action of many carcinogenic factors. At present, breast cancer is a common cancer type among women all over the world, and its morbidity and mortality have increased significantly year by year[14]. According to the research [15], the incidence and death of female breast cancer in China ranked first in the world in 2018, accounting for 17.6% and 15.6% of the incidence and death of female breast cancer in the world respectively. Jing Quan et al. [16] concluded after discussion that ACSLs family members have different roles in cancer occurrence. ACSL1 participates in

TNFα-mediated pro-inflammatory phenotype, and mainly promotes cancer progression. ACSL3 is an androgen response gene. High ACSL3 is expressed in a variety of cancers, including melanoma, triple negative breast cancer (TNBC) and high-grade non-small cell lung cancer (NSCLC), and is associated with poor prognosis of patients with these diseases. According to the specific cancer type and tissue environment, ACSL4 can play an opposite role as a tumor suppressor or oncogene. In addition, ACSL4 plays an important regulatory role in iron sagging. ACSL5 is involved in cell apoptosis induction, and is mainly used as a tumor suppressor of cancer. The down-regulation of ACSL6 has been observed in many cancers. In addition, by listing the clinical therapeutic significance of ACSLs, it is considered that it may be a valuable biomarker and therapeutic target for accurate cancer treatment.

3.1 ACSL1 and Breast Cancer

Many studies have shown that granulocyte-macrophage colony stimulating factor (GM-CSF) is involved in promoting the growth and progress of tumors, while tumor necrosis factor-α (TNF-α) is involved in the induction of GM-CSF in different cells. Reeby Thomas et al. [17] studied the role of ACSL1 in TNFα-mediated GM-CSF production. The results showed that the expression and secretion of GM-CSF mRNA increased after hatching MDA-MB-231 cells with TNFα. Blocking ACSL1 activity in cells with Aspergillus C can significantly inhibit the secretion of GM-CSF. However, GM-CSF is not needed to inhibit β -oxidation and ceramide biosynthesis. The knock-down mediated by small interfering RNA further proved that the production of GM-CSF induced by TNFα was significantly reduced in ACSL1 defective cells. Therefore, it is concluded that ACSL1 plays an important role in the regulation of GM-CSF in TNFα induced MDA-MB-231 breast cancer metastatic cells. Therefore, ACSL1 may be considered as a potential new tumor growth therapeutic target. It has been reported [18] that the high level of TNFα is related to the strong tumor invasion and poor prognosis of breast cancer.

3.2 ACSL3 and Breast Cancer

Yassmeen Radif et al. [19] Through subcellular isolation and analysis of MCF-7 breast cancer cells, the intracellular localization of endogenous expression of ACSL3 was further studied, and it was found that the distribution of ACSL3 closely overlapped with protein involved in transportation from trans Golgi network and endosome. These observations reveal new information about the partition of fatty acid metabolism in cancer cells, which provides useful information for future consideration of treating malignant diseases specifically for any enzyme. Hae Min Jeong et al. [20] found that the mutation of ACSL3 would change the prognosis of patients with triple negative breast cancer (TNBC).

3.3 ACSL4 and Breast Cancer

The release of AA in breast cancer are considered as important signals leading to cell proliferation. AA is transformed into different eicosanoids with biological activity by lipoxygenase (LOX), cyclooxygenase (COX) and cyclooxygenase cytochrome P450. LOX and COX are known to play a key role in tumor growth and metastasis [21,22]. Paula M.Maloberti et al. [21] used a breast cancer cell model to study the relationship between ACSL4 expression and AA in mitochondria, and its role in the production of lipoxygenase and cyclooxygenase metabolites and the development of invasive cell phenotype. The results showed that ACSL4 was the key enzyme of AA production mechanism and AA lipoxygenase and cyclooxygenase metabolites production in mitochondria of breast cancer cells. The overexpression of ACSL4 may promote the proliferation,

invasion and migration of invasive phenotype of breast cancer cells by regulating the production of lipoxygenase and cyclooxygenase metabolites. Anissa Belkaid et al [23] treated ERα-positive MCF-7 and T47D breast cancer cells with hormone deficiency with 17β- estradiol, which resulted in the increase of cellular uptake of polyunsaturated fatty acids (PUFA) arachidonic acid (AA) and eicosapentaenoic acid (EPA). These results indicated that ACSL4 was the target of ERα stimulated by 17β- estradiol, 17β- estradiol induced the proliferation and invasion of estrogen receptor positive breast cancer cells, and increased the level of ACSL4 protein. Silencing ACSL4 eliminated the ability of 17β- estradiol to induce cell migration, proliferation and invasion. Xinyu Wu et al. [24] analyzed the relationship between the expression of ACSL4mRNA in breast cancer cell lines and tissue samples and the presence of steroid hormones and human epidermal growth factor receptor 2(HER2), and used cell lines to evaluate the increase or decrease of ACSL4 expression level. It was found that ACSL4 expression was not only related to the expression of androgen receptor (AR) and estrogen receptor (ER), but also negatively related to the expression of progesterone receptor (PR) and the amplification of human epidermal growth factor receptor (HER-2). This indicates that ACSL4 can be used as a biomarker for AR positive triple negative breast cancer and AR negative quadruple negative breast cancer. Ulises Daniel Orlando et al. [25] used simulated cells and control cells with high expression of ACSL4 to study the role of ACSL4 in the process of anti-cancer drug resistance and the possible mechanism of ABC transporter. Finally, after a series of experiments, it was found that after chemotherapy, the simulated cells had a higher survival rate than the control cells, but this effect could be inhibited by doxycycline or ACSL4 inhibitor induced by shRNA. They believe that ACSL4 combined with chemotherapy is a possible treatment option for patients with high metastatic breast cancer, and it may reduce the toxic and side effects of chemotherapy, and to some extent may prolong their disease-free survival and overall survival.Sebastian Doll et al. [26] found that ACSL4 is the key determinant of iron sagging sensitivity, and ACSL4 can predict the sensitivity of a subset of basal breast cancer cell lines to iron sagging. Finally, pharmacological inhibition proves that ACSL4 may inhibit the iron death process to some extent, and can prevent and treat related diseases.

3.4 ACSL5 and Breast Cancer

MENG-CHI YEN et al. [27] found that ACSL5 was significantly related to good survival rate from gene expression data sets and breast cancer cell lines, which indicated that ACSL5 was a potential new biomarker to predict the prognosis of breast cancer patients. Wei-Ching Chen et al. [28] used PrognoScan and Kaplan-Meier plotter, and the results showed that patients with high expression of ACSL5 had a good survival rate in breast cancer, which means that ACSL5 has an anti-cancer effect in breast cancer. Matteo Rossi Sebastiano et al. [29] found that the low expression of ACSL5 increased the growth of tumor, which indicated that ACSL5 had anti-cancer effect.

3.5 ACS6and Breast Cancer

Marı´a Isabel Castillo et al. [30] reported a case of astrocytoma, thyroid cancer and breast cancer caused by the mutation of ACSL6 gene, which changed the secondary and tertiary structures and disturbed lipid metabolism, indicating that ACSL6 may be related to the occurrence of breast cancer.

4. Conclusions

At present, the traditional treatment methods of breast cancer are mainly surgical treatment, radiotherapy and chemotherapy, supplemented by endocrine therapy and targeted therapy.

However, the above treatment strategies have shortcomings in the treatment process, such as incomplete surgical resection, easy recurrence, large side effects of radiotherapy and chemotherapy, etc., resulting in poor treatment and prognosis of patients [31]. At present, the development of anti-tumor drugs based on tumor metabolic process has attracted the attention of a large number of researchers. Recent studies have shown that the regulatory factors of ACSLs include transcription factors and co-activators, hormone receptors, protein kinases and non-coding RNA, which regulate the metabolic process of cells by mediating fatty acid metabolism. As an independent prognostic factor of cancer prognosis, ACSLs has become a valuable biomarker and potential therapeutic target for clinical diagnosis and treatment of various cancers. ACSLs plays a role in promoting or inhibiting cancer in different cancers, so the design of inhibitors or activators for ACSL family-specific tumor therapy depends on the tumor type. Fat metabolism is one of the three major energy metabolism, which plays an important role in the normal growth and metabolism of cells. They participate in the energy metabolism and cell signaling pathway to maintain the normal function of the body. When fatty acid metabolism disorder leads to excessive synthesis and deposition of lipids, it will induce various diseases. However, ACSLs plays a key role in fat metabolism, and the abnormal expression of ACSLs is closely related to various tumors. At present, however, the research mainly focuses on the effect of ACSLs on fat metabolism, while there are relatively few studies on the regulatory factors of ACSLs expression, among which ACSL3, ACSL4, ACSL5 and ACSL6 are the most significant subtypes, and the related research mainly focuses on animal experiments such as mice and hamsters. At present, the existing research shows that the mechanism of ACSLs participating in the lipid metabolism process of tumor cells and the related regulatory factors still need to be further studied. It is hoped that a thorough understanding of the mechanism of ACSLs regulating lipid metabolism will provide new insights for the diagnosis and treatment of breast cancer.

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