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Research Article

Serine Plays an Important Role in Maintaining the Survival of Tumor Cells

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Abstract: Serine metabolism is becoming more and more important in a variety of cancers. This paper reviews the discovery of serine synthesis pathway and its imbalance in cancer, and the recent research results on serine metabolism in cancer, and also discuss on how serine metabolism plays a role in cancer.

Keywords: Serine; Phosphatase; Glutathione

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1 Introduction

In order to start and progress of cancer, cancer cells need to reprogram their catabolism and anabolism to obtain energy and biomass synthesis, so as to promote their own survival and development. At this stage of proliferation, tumor cells need to overcome the oxidative stress disorder, hypoxia and nutrient deficient microenvironment[1-3]. Although the changes of glucose and glutamine metabolism are the core of cell energy metabolism[4], in the study of Locasale et al., it was found that serine, a non essential amino acid, plays an important role in supporting tumor growth[4-5]. In addition to the role of serine in protein synthesis, serine is also the precursor of other nonessential amino acids glycine and cysteine[6]. Cancer cells not only need ATP and TCA cycles produced by glycolysis to survive, but also need biomass synthesis for cell proliferation under normal and stress conditions; Especially in solid tumors, the destruction of internal tissue structure and lack of vascularization lead to nutritional failure. Serine synthesis pathway (SSP), in the future precision medical trend environment, targeted cancer treatment and intervention can be carried out through these metabolic pathways.

2 SSP and regulatory factors

2.1 SSP

Serine biosynthesis in cells is called serine de novo pathway (SSP), which is closely related to glucose metabolism. 3-phosphoglyceric acid (3-PG), an intermediate product of glycolysis, is an important raw material for serine synthesis.3-PG forms 3-hydroxypyruvate phosphate (3-php) under the action of phosphoglycerate dehydrogenase (phgdh), and 3-php and glutamic acid undergo transamination in phosphoserine Serine-3-phosphate (3-ps) is produced by phosphatase (psat1), and finally 3-ps is metabolized to serine and glycine by phosphatase serine phosphatase (PSPH) and a mitochondrial enzyme shmt2, which are two non essential amino acids in mammals. In addition, glutamate in SSP pathway can be converted to serine through psat1 and PSPH[7-9]. In rapidly proliferating tumor cells, the most important source of serine is ssp. Many cancer types show enhanced serine biosynthesis and import serine from the extracellular environment because they de novo express PHGDH, psat1 and PSPH[10]. In

breast cancer and neuroblastoma, the expression of SSP metabolizing enzyme PHGDH and rate limiting enzyme shmt2 of mitochondrial serine catabolism are positively correlated with each other[11], and it has been reported that the expression of psat1 is related to the proliferation and invasion of pancreatic cancer. Therefore, many modern cancer treatment strategies have targeted 1C unit metabolizing enzymes and nucleic acid metabolizing enzymes downstream of 1C unit metabolic pathway. The attempt of this chemotherapy method is based on the effective remission of hematologic malignancies by anti-folate drugs 70 years ago [12,13].

2.2 Important regulators of SSP pathway

TAp73, ATF4, G9a, Nrf2 and cmyc are reported to regulate serine biosynthesis and metabolism[14-16]. TAp73 knockout completely eliminated the serine / glycine dependent proliferation of cancer cells, suggesting that TAp73 affects the metabolism of glutamine and serine, affects the synthesis of glutathione (GSH), and determines the pathogenesis of cancer[16]. Activating transcription factor 4 (ATF4) is a key transcription factor. Under amino acid starvation, three enzymes in SSP, PHGDH, PSAT1 and PSPH, can be up-regulated simultaneously to adapt to cell stress. At the same time, ATF4 can also activate the expression of downstream SSP metabolic genes, such as shmt2 and mthfd2[17,18]. In the study of black et al[19], the specific marker G9a revealed that the methyltransferase G9a of histone H3K9 is crucial for the transcriptional activation of serine / glycine biosynthesis pathway. Jane Ding[15] and others further confirmed that G9a is an important part of the complex molecular pathway combining serine starvation perception and transcriptional control of serine synthesis. G9a can give tumor survival and growth advantages by increasing the production of serine and its downstream metabolites. ATF4 itself is the transcription target of Nrf2[18] and other factors. In non-small cell lung cancer, Nrf2 promotes ATF4 dependent expression of 1C metabolic genes such as shmt2, providing a substrate for glutathione and nucleotide synthesis. Cmyc can not only regulate the metabolism of glucose, glutamine and nucleotide[20], but also found that the metabolism of serine and glycine is also controlled by cmyc[21] under the condition of nutrition deprivation. Under nutritional starvation, almost all SSP enzymes in hepatocellular carcinoma (HCC) cells are directly activated by CMYC at transcriptional level. Activation of SSP can lead to increased GSH level, new nucleotide synthesis and cell cycle progression.

3 The important role of serine

3.1 Serine and one carbon metabolism

Carbon metabolism refers to the metabolic process in which the organic group containing one carbon atom is transferred to participate in biosynthesis; One carbon metabolism pathway includes three key reaction pathways: folate cycle, methionine cycle and sulfur transfer pathway; The organic group containing one carbon atom is usually called "1C unit". The 1C units in the body include methyl (- CH3), formyl (- CHO) and carbynyl (- CH =), which are usually derived from the metabolites of glycine, tryptophan, serine and methionine. Carbon metabolism is not only the synthetic pathway of amino acids, nucleotides and some important biological substances; At the same time, it can also allocate carbon atoms for various organic compounds needed by biological activities[22].

3.1.1 Serine and folate cycle

Folate cycle is an important metabolic pathway that meets many cancer specific nutritional needs. The 1C unit of serine is transferred to tetrahydrofolate (THF) by serine hydroxymethyltransferases (shmts) to form 5,10 methyltetrahydrofolate (ch2-thf). The 1C unit is then transferred from one location of the THF to another, creating a folate cycle. Folate cycle produces other metabolites essential for cell growth, including nucleotides, methionine and antioxidant reduced coenzyme II (NADPH), through the transfer of tetrahydrofolate and its derivatives between the carbon units in the cytoplasm and mitochondrial compartment[23].

3.1.2 Serine and methionine cycle

Methionine cycle provides methyl units for various reactions such as protein, DNA, RNA and lipid methylation, thus regulating its biological function[24,25]. Adenosylmethionine (SAM) is a major methyl donor molecule in cell methylation reaction, which is directly synthesized from essential amino acid methionine. Folate metabolism can donate 1C units to Sam pool, and serine derived 1C units can also be used to support Sam synthesis; Although in many cancer cells, the way of supplying 1C units

from folate cycle to methionine cycle seems to have low level activity, the study of Maddocks et al found that serine availability is still needed to maintain Sam level[26]. These results indicate the complex relationship between serine metabolism, nucleotide synthesis and Sam, and illustrate that serine restriction can have harmful effects on tumor cells as a new way.

3.1.3 Serine and sulfur transfer pathway

The redox balance of serine is also related to its contribution to glutathione production. Cells can control the level of glutathione through their own synthesis and transport. Glutathione is synthesized by cysteine, glutamic acid and glycine in two ATP dependent steps in the cytoplasm, which can be transported to various cell compartments. Homocysteine and serine are precursors of cysteine synthesis. There are two steps in this pathway: 1) cystathionine β - synthase (CBS) condenses serine with homocysteine, an intermediate of methionine cycle, to form cystathionine; 2) Cystathionine can then be cleaved by cystathionine gamma lyase (CTH) to release cysteine[27]. In the process of mutual conversion of compounds in this cycle, antioxidant glutathione can be produced. Since glycine and cysteine are products of serine metabolism, and the activation of SSP allows glucose derived carbon to be guided to glutathione synthesis for antioxidant defense, the new synthesis of serine in cells can affect the reduction level of glutathione[28].

3.2 Serine and cell stress

Glycine and cysteine are the products of serine metabolism, while glutathione is a tripeptide composed of glycine, glutamic acid and cysteine. Serine can indirectly affect the level of intracellular glutathione to achieve the purpose of scavenging reactive oxygen species and promoting the redox balance in cells[29-31]. In serine starvation, p53 activates p21 to promote the production of glutathione to combat reactive oxygen species (ROS)[32,33]. In addition to glutathione, NADPH is also a key antioxidant molecule, which can provide reducing capacity[3,34] for biosynthesis and buffer oxidative stress in rapidly proliferating or isolated cells. Fan J et al. Also proposed that SSP metabolism can regulate redox balance in a specific way[35, 36]: The first available pathway in mitochondria is serine catabolism, and then output 1C units to support the cytoplasmic anabolism and maintain the level of NADPH. The reason may be that there is a specific NAD (P) H / NAD (P) ratio between compartments, which is more conducive to the oxidation of 1C unit in mitochondria and the reduction of 1C unit in cytoplasm.

3.3 Serine and tumor proliferation and invasion

One of the main metabolic tasks of non-proliferating cells is to fully oxidize and store nutrients, and then generate energy in the form of ATP. In contrast, proliferating cells must accumulate the biomass needed to build new cells, including genome replication and ribosomal RNA nucleotides, membrane lipids, protein amino acids, and other cell building modules. The biosynthesis of these macromolecules requires not only ATP, but also carbon and nitrogen precursors[37], as well as electron acceptors[38]. The metabolic characteristics of cancer cells described the correlation between glycine consumption and cancer cell proliferation rate[8]; However, Labuschagne et al Showed that serine is the fastest consumed amino acid to support proliferation, and some cells may switch to glycine metabolism mode only when serine is depleted[39]. It has even been observed that in some cells, high levels of glycine may damage cell proliferation, depending on the relative availability of serine and 1C units. The rate and direction of these units driving shmt1/2 reaction may be necessary to support optimal cell proliferation. The mechanism may be that inhibition of shmt2 reaction products or reverse action of shmt1 leads to "waste" of cell 1C pool. Thus, the mechanism of nucleotide synthesis is impaired[35]. Zhang et al found that PHGDH was highly expressed in poor prognosis of lung adenocarcinoma[40]. By linking serine metabolism with glutathione and pyrimidine, the cell culture model with high level of PHGDH showed a rapid proliferation phenotype. As metabolism is a highly complex network with many compensatory mechanisms, many invasive tumor cells show not only dependence on glucose metabolism, but also up regulation of one carbon metabolism after glucose deprivation to make them survive[41].

4 Clinical prospects

Stem cells (SCS) maintain tissue homeostasis by balancing self-renewal and differentiation. As a key regulator of cell fate in the process of tumor

initiation and growth, dietary serine restriction will destroy the maintenance of SCS. It is proposed that targeted serine uptake may be a promising therapeutic approach to eliminate carcinogenic SCS[42]. Nevertheless, there is reason to hope that a therapeutic window can be achieved to selectively target cancer cells. In recent years, researches on inhibitors of PHGDH, the first rate limiting enzyme of SSP pathway, have become more and more popular. Cbr-5884 is a PHGDH inhibitor identified from 800000 drug like compounds library, which can inhibit the proliferation of cancer cells addicted to serine synthesis. However, the specific binding mechanism of cbr-5884 to PHGDH and its role in vivo are still unclear[43,44]. Subsequently, foreign research team screened small molecule repository (mlsmr) and found that nct-503 compound could inhibit the transformation of serine into nucleotide and inhibit tumor proliferation by inhibiting PHGDH enzyme activity[45] and reducing the incorporation of intracellular and extracellular carbon. In addition, in the attempt to treat patients with small molecule PHGDH inhibitors, if the inhibitors cross the blood-brain barrier, the possible neurological symptoms must be considered[6]. De Koning et al Showed that in the serine synthesis pathway, although the deletion of the first enzyme phosphoglycerate dehydrogenase (PHGDH) could not prevent development, PHGDH deficient mice suffered from severe neurological defects at birth and died soon after birth[46]. In the absence of serine, exogenous glycine uptake can not support nucleotide synthesis[39]. Cancer cells will selectively consume endogenous serine and convert serine into glycine and 1C units in cells to construct nucleotides. How to best identify patients who may respond to PHGDH inhibitors remains an important issue, because not all cancer cells depend on SSP. Not only the inhibitors of SSP pathway have great clinical research value, but also PSPH, the second rate limiting enzyme of SSP pathway, can be used as a marker of certain cancer. The expression of PSPH in HCC patients is higher than that in adjacent normal tissues. It is suggested that PSPH is the rate limiting enzyme of hepatocellular carcinoma, and abnormal PSPH level can predict the mortality of HCC patients[21]. The discovery of PSPH may be a potential biomarker for the prognosis of HCC.

Most modern cancer medical researches focus on this disease from the perspective of gene. However, cancer also involves biochemical metabolic mutations, such as adaptive metabolic rearrangement to support the proliferation of cancer cells that are different from normal cells. Metabolic flux changes or transforms into malignant state after specific oncogene expression, and makes relatively rapid response to changes in nutrient supply and tissue environment[43,47-49]. Serine metabolism is becoming more and more important in a variety of cancers. How this amino acid metabolism affects cancer phenotype is an active research field. It brings hope for the treatment of patients by studying the specific metabolic needs of cancer cells.

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