Implications of One-Carbon and Polyamine Metabolism for Cancer

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Contributor: Anowarul Islam , Zeeshan Shaukat , Rashid Hussain , Stephen L. Gregory

Cancer metabolic reprogramming is essential for maintaining cancer cell survival and rapid replication. A common target of this metabolic reprogramming is one-carbon metabolism which is notable for its function in DNA synthesis, protein and DNA methylation, and antioxidant production. Polyamines are a key output of one-carbon metabolism with widespread effects on gene expression and signaling. One-carbon metabolism includes the methionine cycle, which is linked to the folate cycle, polyamine synthesis, and the trans-sulphuration pathway.

methionine cancer polyamines

1. Folate Metabolism and Cancer

Due to its range of roles in protein and DNA synthesis, methylation processes, and redox homeostasis, folate metabolism can contribute to oncogenesis. In tumor treatment, drugs that specifically target folate metabolism have been employed frequently, particularly against dihydrofolate reductase (DHFR) [1]. These inhibitors stop the growth of cancer by preventing the production of nucleic acids, which are needed for DNA replication and cell proliferation. DHFR inhibitors block the production of tetrahydrofolate, which thus inhibits purine and thymidylic acid synthesis [1]. However, antifolate medications have an adverse effect on normal cells when used to treat cancer because one-carbon metabolism is also required for healthy cells, particularly in the immune system. Nonetheless, numerous cancers have been treated with DHFR inhibitors, such as methotrexate, which was introduced in 1947 but is still very widely prescribed. Like other chemotherapeutic treatments, these drugs may fail because cells develop resistance by, for instance, impairing drug absorption, decreasing drug retention inside the cell, and decreasing drug affinity [2]. There is a need to develop further therapies that specifically target folate metabolism.

In a review of the mRNA profiles of 1981 tumors, MTHFD2 and SHMT2 were shown to be among the top five genes with the highest levels of expression, demonstrating the carcinogenic influence of mitochondrial folate metabolism [3][4]. Similar studies on the mitochondrial folate metabolism enzymes revealed a link between cancer and aberrant SHMT2 and MTHFD2 expression [5][6]. Aberrant SHMT2 and MTHFD2 expression might impair DNA synthesis and damage redox balance, which is important for cancer cell survival [7]. Other folate metabolism enzymes, such as SHMT1 and MTHFD1L, have also reportedly been linked to cancer. Disrupting SHMT1 interferes with the incorporation of dUMP into DNA, causing DNA double-strand stability to be disturbed [8]. Additionally, ovarian cancer is prevented from spreading and growing by SHMT1 knockdown [8]. Lung cancer cells are also affected by SHMT1 knockdown [9]. According to a recent study, MTHFD1L knockdown caused tongue squamous cell carcinoma cells to die under redox stress via lowering the concentration of NADPH [10]. These

results suggest that folate metabolism is a desirable target for the therapy of cancer if the problems of toxicity and resistance can be overcome.

2. Serine Metabolism in Cancer

Changes in serine metabolism may have significant consequences that may lead to the development of cancer as well as other illnesses [11][12]. Serine can be absorbed by the cell or produced by the serine synthesis pathway from glycolytic intermediates. It has long been recognized that serine, whether from diet or generated endogenously, is linked to cancer, and actively promotes its growth [13][14]. Serine can also be produced by breaking down cell proteins, such as through autophagy, and by converting glycine [15]. The process of serine synthesis (SSP) is one of numerous glycolysis side branches that allows carbons obtained from glucose (or pyruvate under gluconeogenic circumstances) to be redirected to the production of serine and is upregulated in many cancers [16]. Glucose is the primary source of carbons for de novo serine synthesis in people and rats that are well-fed, but under starving conditions, gluconeogenesis can contribute up to 70% of the total serine produced [17].

Serine is necessary for the creation of phospholipids such as sphingolipids and phosphatidylserine, as well as other amino acids like cysteine and glycine. Serine is a key methyl donor, though there are many other ways that cells can obtain one-carbon groups, including choline, betaine, glycine, histidine, sarcosine, and the formate that is produced when tryptophan is broken down [18][19]. Studies in yeast and mammalian cells revealed that serine catabolized in the mitochondria is the source of the majority of the cytosolic one-carbon units [8][20][21], and blocking one-carbon metabolism in both the mitochondria and cytoplasm precludes cell growth [16].

Serine's role in generating methylene-THF makes it a key contributor to avoiding the toxic consequences of homocysteine build-up. Homocysteine is the link between the transsulfuration pathway and the methionine cycle, and the building blocks for the synthesis of cysteine are homocysteine and serine. Serine depletion results in lower amounts of glutathione [22] because glycine and cysteine are by-products of serine degradation, whereas activation of serine synthesis enables glucose-derived carbon to be channeled towards glutathione synthesis for antioxidant defense [11][23]. This has implications for tumor oxidative stress tolerance that have not been fully examined (see 4.2 below).

3. SAM-S Metabolism in Cancer

Methionine, which makes up half of the body's daily requirement for amino acids, is the primary amino acid used in the liver to produce SAM [24][25]. SAM is produced by MAT (SAM synthase) from methionine in an ATP-dependent mechanism [24]. The adenosyl moiety of ATP is combined with methionine during this process to change it into a high-energy reagent that can carry a sulphonium ion. SAM can then transfer a methyl group to a variety of substrates, including proteins, DNA, RNA, and lipids [26]. The cellular level of SAM can be affected by impaired dietary intake, absorption, transport, metabolism, or enzymatic processing of methionine [27][28][29][30]. For instance, dietary methionine limitation lowers SAM levels and increases the longevity of certain species [31][32][33].

Because cancer is frequently characterized by abnormal methylation states and methionine or SAM dependency, SAM has been explored as a therapeutic target in the treatment of cancer [34][35]. For example, rats have been used in tests to determine how SAM treatment affected the growth of neoplastic liver lesions. The percentage of the liver that was occupied by GST-P-positive lesions significantly decreased when SAM was administered to rats during the clonal expansion of initiated cells (promotion), primarily as a result of a reduction in the size of the lesions [36][37][38][39][40][41][42]. The number and size of liver nodules decreased after receiving the same SAM doses for 11 weeks [36][37]. A consistent decrease in incidence and multiplicity of neoplastic nodules could be observed when SAM medication was continued for up to six months [43]. On a cellular level, SAM's chemopreventive action is linked to an increase in remodeling and a dose-related reduction in DNA synthesis in preneoplastic and neoplastic lesions [36][40][41]. Additionally, rats given SAM showed an increase in apoptosis in neoplastic nodules and hepatocellular carcinoma [37][40]. SAM therapy decreased carcinogenesis and metastasis in vivo while increasing apoptosis and decreasing the proliferation and invasiveness of breast cancer cells in vitro [44]. SAM treatment has been shown to be effective in inhibiting the proliferative and invasive potential of many cancer cell lines [45][46]. SAM selectively inhibits the proliferation and invasiveness of liver cancer cells by changing the transcriptome and methylome [47]. Although SAM has positive impacts on the treatment of cancer, more research is needed to establish SAM as a cancer therapy, as in many cases, the specific metabolic changes responsible for the observed anti-cancer effects are unclear.

4. Methionine Dependency in Cancer

Methionine metabolism and cancer have been linked on several levels. Even though they easily convert homocysteine into methionine, the majority of cancer cells are unable to proliferate if methionine in the media is replaced by homocysteine. Surprisingly, intracellular methionine levels in breast cancer cells remained substantially stable when they were transferred to homocysteine media and analyzed; however, in this situation, SAM levels were strongly depleted [48]. Homocysteine substitution for methionine has no effect on non-cancerous cells, suggesting they have less need for SAM. Cancer and normal cells are different in their growth rates with different metabolic needs, so it is frequently challenging to interpret the differences between the metabolic dependencies of normal and cancer cells. Perhaps unsurprisingly, there are some methionine-independent tumor cell lines, and in these cases, SAM levels are relatively normal [49][50].

According to the Hoffman effect, methionine is metabolized differently by cancerous and non-tumorigenic cells. Using ^{11}C-methionine positron emission tomography, human cancers may be easily seen and distinguished from normal tissue, demonstrating this higher need (Met-PET). Met-PET imaging often outperforms 18F-deoxyglucose PET (FDG-PET) imaging, particularly in glioma, as the increased brain glucose metabolism interferes with tumor-specific FDG signals. However, multiple myeloma and other malignancies have also been studied with Met-PET [51].

5. Homocysteine Metabolism and Cancer

Hyperhomocystinuria and cancer have been shown to be closely related by recent scientific developments. Homocystinuria is defined by a rise in the level of homocysteine (Hcy) in the serum and can come from an inborn mistake in the metabolic pathways of sulfur-containing amino acids [52]. Cancer patients have also been found to have increased plasma homocysteine concentrations. There are strong clinical correlations between a number of polymorphisms in the enzymes implicated in the Hcy detoxifying pathways and various cancer types [53][54][55][56][57][58][59][60][61][62][63]. Many cancer types exhibit high plasma Hcy levels in the advanced stages, although there may be little to no change in plasma Hcy levels in the earlier stages of the disease [55][64][65][66][67][68][69][70][71][72][73]. Why the Hcy levels differ between the early and late stages of cancer is unclear. However, since Hcy promotes the growth of cancer cells [74], increased generation and secretion of Hcy seems likely to be an adaptive metabolic mutation acquired during cancer progression. Caco-2 cell lines with higher homocysteine levels exhibit greater cellular proliferation. By including more folate in the culture media or by supplementing it with its metabolites, such as 5-MTHF [75], this increased proliferation can be reduced. However, because a very high Hcy concentration may potentially be lethal to the cancer cells, advanced-stage cancer cells may release Hcy. Clinically, the situation is less clear—in some studies, there is no evidence of a correlation between Hcy levels and cancer risk [76]. Further investigations are required to reveal the precise mechanism of how cancer patients deal with Hcy metabolism.

6. The Role of One-Carbon Metabolism in Nucleotide Synthesis in Cancer

The synthesis of purine and pyrimidine nucleotides, which are required for the synthesis of DNA and RNA, depends on the one-carbon cycle [77]. A single carbon, typically from serine, is transferred during one-carbon metabolism to create the pyrimidine and purine bases [34], hence the significance of serine in the production of nucleotides. During glycolysis, serine is produced from 3-phosphoglycerate (3-PG) [78]. Serine-derived one-carbon transfer to tetrahydrofolate results in 5,10-methylenetetrahydrofolate (CH2-THF), a substance essential for the synthesis of pyrimidines [79]. CH2-THF is also the methyl donor used to regenerate methionine from homocysteine, so there is a balance between its use in pyrimidine synthesis versus providing the methyl group to SAM for use in DNA or protein methylation, polyamine synthesis, or the generation of glutathione.

The subsequent transformation of CH2-THF into 10-formyltetrahydrofolate (CHO-THF) is an essential component of purine synthesis [79]. Therefore, the synthesis of both pyrimidines and purines depends on a carbon donor such as serine and the tetrahydrofolate carrier. Due to the need for a large quantity of DNA nucleotides, one-carbon metabolism is crucial for cancer cells to proliferate quickly. As a result, one-carbon metabolism is a prospective target for reducing cell growth. It was shown that lowering serine levels or blocking particular mitochondrial folate metabolic enzymes decreased the number of purine nucleotides, which in turn prevented proliferation [22][80][81]. As a result, researchers are actively looking at anticancer medications that target one-carbon metabolism [82][83].

7. Polyamine Metabolism in Cancer

Prostate cancer cell proliferation and differentiation, often controlled by androgen hormones, are correlated with levels of polyamines, particularly spermine [84] which is plentiful in the human prostate. Spermine may serve as a biomarker to distinguish between low-grade and high-grade prostate cancers because its content is lower in the latter [85]. In prostate cancer, the most significant metabolic disturbance observed was increases in polyamine metabolites and in dcSAM [86]. The PTEN-PI3K-mTOR complex 1 (mTORC1) pathway was shown to regulate the stability of SAMDC (AMD1), which controls the use of SAM for polyamine synthesis in prostate cancer [86][87]. Inhibitors of mTORC1 or SAMDC were able to significantly impede growth in prostate cancer cell lines, and this could be partly rescued by supplementing with spermidine. In this case, the role of ODC1 in polyamine regulation downstream of mTORC signaling was excluded—it was just via SAMDC regulation. However, in c-MYC transgenic mice, c-MYC has been shown to promote prostate cancer carcinogenesis by boosting polyamine production through the transcriptional control of ODC [88]. This is significant because ODC1 has been identified as a c-Myc-responsive rate-limiting step in polyamine synthesis [89]. Notably, PGC-1α inhibits c-MYC and hence ODC, which reduces polyamine production and lowers the aggressiveness and spread of prostate cancer [88]. By contrast, the androgen receptor typically acts in prostate cancer to upregulate ODC1 expression [90], and indeed ODC1 overexpression alone may be enough to drive prostate tumorigenesis [91].

Similar to the observation in prostate cancer, human breast cancer tissue has a lot more acetylated polyamines than healthy breast tissue [92]. In breast cancer patients, estrogen signaling is linked to the creation of polyamines and purines. Estrogen directly contributes to the progression of breast cancer by activating the estrogen receptor (ERα), which binds to estradiol (E2) [93]. Through the mitochondrial folate route, this binding activates ERα and causes the activation of genes that boost polyamine and purine production [93][94]. Additionally, due to their effects on the activity of the insulin receptor, polyamines may control the mitogenic action of insulin in breast cancer [95]. ODC mRNA and protein levels are markedly increased in breast cancer patients, and they positively correlate with the tumor, node, and metastases (TNM) stages of the disease. Increased ODC activity is linked to higher cancer cell proliferation rates and a worse prognosis for breast cancer patients [96]. Arginase, which changes arginine into ornithine [97][98], is more prevalent in breast cancer, making it a potential market for breast cancer in its latter stages [99]. In addition to ODC, breast cancer also exhibits increased levels of ADC and agmatinase, enzymes involved in the synthesis of putrescine from arginine [100]. Early in metastasis, arginase and polyamine production are increased [101]. These considerations are relevant to this research because, in each of these cases in which polyamines are elevated in cancer, SAM and the one-carbon cycle are required for their synthesis.

Patients with pancreatic cancer have polyamines found in their urine, serum, and saliva, which makes them potential biomarkers [102][103][104][105]. In human pancreatic ductal adenocarcinoma (PDAC), KRAS mutations are the most prevalent (representing around 95% of all mutations) [106]. In addition, the copy number of c-MYC has increased in more than 50% of human PDAC cell lines [107]. Similar to other cancers, KRAS and MYC are upstream activators of polyamine production in PDAC [106][108]. ODC levels rise in pancreatic cancer and aid in the development and spread of advanced pancreatic cancer [109][110][111]. Employing an ODC inhibitor (DMFO) and a polyamine transport inhibitor (Trimer44NMe) together greatly decreased the survival of PDAC cells by inducing apoptosis [108]. Immune privilege must be established in order for the PDAC tumor to survive, and spermine is critical for this process [112].

Poor prognosis is linked to the dysregulation of polyamines in neuroblastoma, and various polyamine homeostasis-related genes are transcriptional targets of cMYC/MYCN [113][114][115]. The modulation of the SLC3A2 polyamine exporter and other essential elements of the polyamine pathway in vitro is directly induced by MYCN, leading to increased polyamine production and accelerated neuroblastoma cell proliferation [116]. ODC has been recognized as a potent oncogenic transforming factor, and in neuroblastoma, it is the most well-studied target of the transcription factor c-MYC/MYCN [115][117][118]. In vivo neuroblastoma cell proliferation and MYCN-mediated oncogenesis are both reduced in animal models when ODC is disabled [119]. Along with ODC, SAMDC is a target of MYCN and plays a significant role in the growth of neuroblastomas [120][121]. In murine neuroblastoma, S-adenosylmethionine synthetase overexpression is linked to the development of treatment resistance [120]. Transgenic mice used in a preclinical study that used polyamine antagonist regimens targeting ODC1 and SAMDC had their neuroblastoma initiation reduced [122][123].

Metabolic enzymes and polyamine levels affect both treatment and prognosis in leukemia [124]. High levels of polyamines are linked to a bad prognosis in leukemia cells. However, polyamine depletion in healthy cells also results in cell cycle arrest, highlighting the need to preserve polyamine homeostasis. Patients with acute lymphoblastic leukemia (ALL) have increased ODC activity and putrescine levels, and their recurrence can be detected by increased spermine levels in erythrocytes [124].

Polyamine depletion is a plausible approach to decreasing polyamine levels in cancer. Overexpression of the polyamine acetyltransferase SSAT drives the first step of polyamine breakdown and can result in diminished cell growth, migration, and invasion by blocking AKT and GSK3b signaling [125]. These findings were made using a variety of colon carcinoma cell models and human hepatocellular malignancies.

It is not new to use polyamines and their metabolites as cancer biomarkers [126]. In lung and liver malignancies, polyamines and their metabolites in the urine and plasma can be helpful both for diagnosis and as indicators of tumor development [127][128]. Diacetylspermine has been linked to lung and ovarian cancers as a reliable urine biomarker [129][130][131]. Right-side colon tumors associated with biofilms have also been shown to contain significant quantities of diacetylspermine [132][133]. Urinary or serum measurements of polyamines and polyamine metabolites have demonstrated potential as biomarkers for colon, pancreatic, and prostate malignancies [102][134][135][136][137]. The development of more individualized methods for cancer diagnosis and therapy based on the use of polyamines as biomarkers may be aided by such analyses in conjunction with increasingly accurate genetic signatures.

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