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Commentary

Exploiting methionine restriction for cancer treatment

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ABSTRACT

Normal cells can synthesize sufficient methionine for growth requirements from homocysteine and 5-methyltetrahydrofolate and vitamin B12. However, many cancer-cell types require exogenous methionine for survival and therefore methionine restriction is a promising avenue for treatment. While the lack of the methionine salvage enzyme methylthioadenosine phosphorylase (MTAP) deficiency is associated with methionine dependence in cancer cells, there are other causes for tumors to require exogenous methionine. In this review we describe studies that show restricting methionine to certain cancers by diet or by enzyme depletion, alone or in combination with certain chemotherapeutics is a promising antitumor strategy. The basis for methionine dependence in tumor cells is also briefly reviewed.

1. Introduction

A large number of studies have documented the beneficial effect of methionine restriction on increasing life span, improving metabolism and preventing or inhibiting cancer cell growth [1–10]. Despite the encouraging anticancer effects of methionine restriction noted in animal models, clinical studies using methionine restricted diets are limited. More promising may be the use of a methionine depleting enzyme, methioninase.

Methionine is a component of dietary proteins and breakdown in the small intestine generates free methionine that is absorbed and subsequently used for protein synthesis and is also converted to to S-adenosylmethionine a crucial methyl group donor for numerous reactions including DNA methylation and metabolic reactions (Fig. 1). Methionine is synthesized by the ubiquitous methionine synthase in a reaction that requires vitamin B12 (methyl cobalamin) and 5-methyltetrahydrofolate (5-MTHF) as cofactors and is also synthesized in the liver by betaine methyl transferase.

2. Possible causes for methionine dependency in tumor cells

This topic has been reviewed in detail recently [11–13], and a brief review is given below.

2.1. The lack of intracellular methionine salvage in some tumors

Methionine is salvaged from methylthioadenosine (MTA) generated from polyamine metabolism by the enzyme methylthioadenosine phosphorylase (MTAP) and subsequently through additional reactions (Fig. 2). Many tumor cells lack MTAP, either due to deletion of the gene, often co-deleted with the tumor suppressor p-16 (INK4a), or by promoter methylation [14]. As MTAP is also essential for salvage of adenine, MTAP deficient cells have also been shown to be more susceptible to de novo inhibitors of purine synthesis as well as to methionine depletion [15–17].

2.2. Defective methionine synthesis

Some tumor cell types have low levels of methionine synthase and this has been suggested as a cause for methionine dependency [18–21]. A revertant cell line from a methionine dependent cell line that now was methionine independent had increased methionine synthase activity, indicating that low levels of methionine synthase could explain methionine dependence [22].

Rapidly proliferating tumor cells may exhibit an increased requirement for methionine to meet the demands for protein synthesis and trans-methylation that cannot be met by endogenous synthesis, leading to methionine dependence [18,23–26].

Mutations of methylene tetrahydrofolate reductase leading to decreased activity of this enzyme may also affect the cell's requirement for exogenous methionine. This enzyme generates 5-methyl tetrahydrofolate, the substrate for methionine synthesis [27].

The methionine synthase enzyme also requires methyl-cobalamin as a critical cofactor. Impaired provision of cobalamin to methionine synthase has been reported to result in methionine dependence [28,29].

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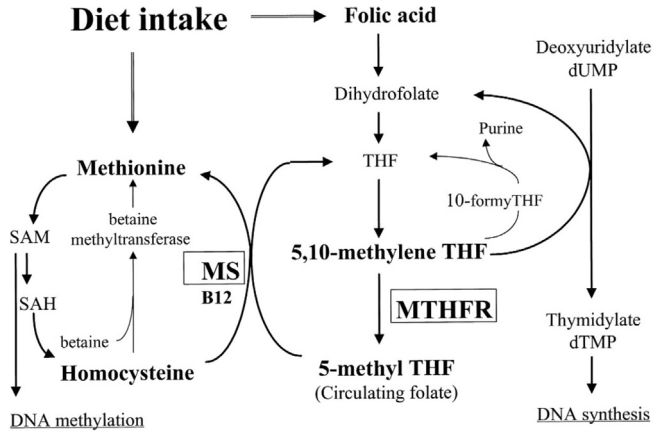

Fig. 1. Methionine metabolism (53), Methionine synthase (MS) forms methionine from homocysteine and 5-methyltetrahydrofolate (5- methyl THF) and vitamin B12. Methionine is used for protein synthesis and is also converted to S-adenosylmethionine (SAM). SAM is a crucial methyl group donor for numerous reactions including DNA methylation. S-adenosylhomocysteine (SAH) is generated from SAM by methyltransferase reactions and is converted to free homocysteine and adenosine. Homocysteine is either converted back to methionine or it enters the cysteine synthesis pathway. Betaine-homocysteine methyltransferase (BHMT) converts betaine and homocysteine to dimethylglycine and methionine, respectively. In a reaction catalyzed by thymidylate synthase (TYMS), the hydroxymethyl group of 5, 10-methyleneTHF is transferred to deoxyuridine monophosphate (dUMP, deoxyuridylate) to generate deoxythymidine monophosphate (dTMP, deoxythymidylate). This reaction generates dihydrofolate (DHF), which is then converted to tetrahydrofolate (THF) by dihydrofolate reductase(DHFR).

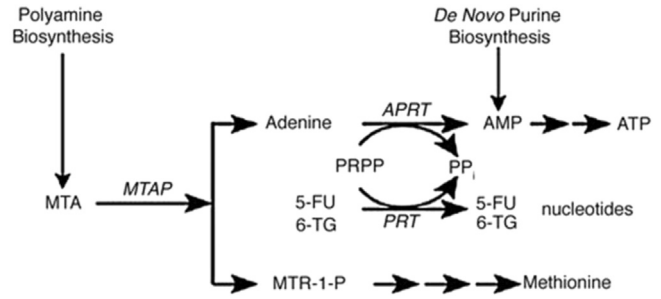

Fig. 2. MTAP metabolic pathway (14). Methylthioadenosine (MTA), a by-product of polyamine synthesis is converted by mthylthioadenosine phosphorylase (MTAP) into adenine and 5-methylthioribose-1-phosphate (MTR-1-P). Adenine is further converted to AMP by the enzyme adenine phosphoribosyltransferase (APRT) and then to ATP. AMP is also produced in cells by de novo purine biosynthesis. The phosphoribosyl group is donated by phosphoribosyl-1-pyrophosphate (PRPP). MTR-1-P is converted by a series of steps to methionine.

2.3. PI3KCA mutations and methionine deficiency

Breast cancer cells with activating mutations of P13KCA had decreased expression of the SLC7A11 gene that encodes the cysteine transporter [30]. As a consequence of decreased uptake of cysteine, homocysteine was diverted to produce cysteine through the trans-sulfuration pathway, resulting in less methionine synthesis from homocysteine.

3. Methionine deprivation as an anticancer strategy

Preclinical studies. Sugimura et al. was the first to report anti- tumor effects of methionine -restriction in the Walker-256 carcinosarcoma tumor in Sprague–Dawley rats using a diet lacking methionine [30]. Animals were force fed diets lacking individual amino acids; diets lacking in valine, isoleucine or methionine showed decreased tumor growth. Further studies explored different methods for reducing methionine intake as an antitumor strategy, i.e., a methionine deprived diet [1,31], parenteral nutrition lacking methionine [32,33], or use of a methionine depleting enzyme, L-methionine-alpha-deamino-gamma-lyase (methioninase) [34,35].

If both methionine and homocysteine are deficient in diets, prolonged use, as shown in a study in female C57BL mice with implanted BW10232 adenocarcinomas, resulted in rapid loss of body weight and death [37]. A Met^{-}/Hcy^{+} diet is better tolerated as normal cells can synthesize sufficient methionine from homocysteine and methyltetrahydrofolate/B12 to meet methionine requirements as shown in a study of sarcoma-bearing mice in which tumor regression occurred with normal performance status of mice [1]. Methionine restriction was also shown to inhibit colonic tumor development in azoxymethane treated F344 rats [3]. The methionine analog, ethionine was ineffective against mice bearing Yoshida tumors, but synergistic anti tumor activity was observed when ethionine administration was combined with dietary methionine restriction [36]. In the TRAMP mouse model of prostate cancer, methionine-restriction resulted in a 50% decrease in prostatic intraepithelial neoplasia [38]. Total parenteral nutrition containing a D-methionine solution in place of l-methionine also inhibited tumor growth in AH109A hepatoma-bearing rats [39]. Animal studies have showed that methionine depleted diets may also decrease the metastasis of cancer cells [1,2,32,36].

Methionine restriction and chemotherapy. Enhanced anti-tumor activity resulted when vincristine [40] or 5-fluorouracil was combined with total parenteral nutrition (TPN) lacking methionine [41]. In a study of N-methyl-N′-nitro-nitrosoguanidine (MNNG) induced gastric cancer, rats were treated with dietary restriction and 5-fluorouracil. The average survival time was 18.6 days in methionine-containing TPN group, 31 days in methionine -deprived TPN group, 27.5 days in methionine -containing TPN + 5-FU group, and 43 days in methionine-deprived TPN + 5-FU group [42].

Methioninase. The encouraging results noted above showing tumor inhibition in rodent models have prompted the discovery of methioninase, an enzyme that metabolizes methionine as a more effective and rapid method to deplete serum methionine. Methioninase has shown efficacy against human tumors propagated in nude mice, either administered alone or in combination with chemotherapy [43–45]. Recent studies in patient-derived orthotopic xenograft (PDOX) models of various recalcitrant cancers have also shown efficacy of methioninase alone and in combination with chemotherapy [45–46]. Recombinant methioninase and chemotherapeutic regimens slowed the growth of Daoy, SWB77, and D-54 brain tumor xenografts in athymic mice, associated with the depletion of mouse plasma methionine. Plasma methionine after treatment decreased to levels below 5 microM for several days. Wide spread necrosis in tumors was noted with methionine depletion [49].

Other uses of methioninase to augment antitumor effects also show promise. For example the prodrug selenomethionine is converted to methylselenol by methioninase, which causes oxidation of thiols to generate toxic superoxide [54]. The vasculature of tumor endothelial cells has been targeted by fusion of methioninase to annexin V to target phosphatidylserine expressed on the endothelial cells. Subsequent administration of selenomethionine by the tightly bound methioninase generated methylselenol and caused marked endothelial cell death with limited toxicity of the prodrug alone [55].

4. Clinical studies

Despite the preclinical studies (vide supra) showing antitumor efficacy of methionine restriction by diet or methioninase, except for one controlled randomized study [41], most other clinical studies reported to date are pilot studies and are limited in number [31,50–52]. Rodent studies are easily controlled using methionine-restricted diets, however,